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ACUTE HEMORRHAGE FROM PEPTIC ULCER*

A Follow-up Study of 310 Patients

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ACUTE hemorrhage is an important and dramatic complication of peptic ulcer. Although there is an extensive bibliography concerning individual bleeding episodes, only a few studies have been reported on the part played by acute hemorrhage in the natural history of the disease.[1-5] Those which have been made have been follow-back or historical in character and with nonuniform methods of study. The value of these studies as an aid in prognosticating the future of such patients is questionable.

Because of this scarcity of information, it was decided to follow a group of patients who were known to have had at least one acute hemorrhage due to peptic ulcer and to determine their rates of subsequent hemorrhage and death over a period of years.

CASE MATERIAL

A review of the records of the University Hospitals in Cleveland revealed 310 patients with proved peptic ulcer in whom manifest acute hemorrhage occurred immediately before or during hospitalization in the years 1936-1948. Selection of these records resulted from examination of all hospital charts carried in the cross-index file with diagnoses of peptic ulcer with gastrointestinal hemorrhage, peptic ulcer and gastrointestinal hemorrhage. The diagnosis of peptic ulcer was established shortly before or after hemorrhage by x-ray, surgical or pathological examination. The diagnosis of acute manifest hemorrhage was established by the presence of at least two of the following three criteria: a history of sudden hematemesis or melena, or both, occurring shortly before or during hospitalization; the presence of anemia (red-cell count of less than 4,000,000 and hemoglobin of less than 10.5 gm. per 100 ml.) within three days of the hemorrhage; and the presence of blood in the stools determined by gross examination or a strongly positive chemical test or both. Eighty-nine per cent of the patients had all three manifestations.

METHOD OF STUDY

For each patient the first hemorrhage treated in the University Hospitals between January 1, 1936, and December 31, 1948, was called the index hemorrhage, and the date of that hemorrhage was taken as the date of the patient's admission into the study. It was also at the time of this hemorrhage that the diagnosis of peptic ulcer was established or confirmed. An effort was made to ascertain the course of the disease in each patient up to July 1, 1951, and patients were considered to be satisfactorily followed if an uninterrupted course could be established from the date of entry into the study (the index hemorrhage) until July 1, 1951. The follow-up information was obtained by either personal interview or written word from the patient, personal physician or a responsible family member who had full knowledge of the patient's health. The specific information sought was whether or not the patient had survived to the end of the study period together with an account of bleeding episodes and operations for peptic ulcer between the index hemorrhage and July 1, 1951. When the patient had been admitted to a hospital because of an intervening acute bleeding episode or operation, a diligent effort was made to confirm this fact from the hospital concerned. Date and cause of death, for persons who died before the end of the study period, were verified either by hospitals or from some official death certificate.

For analysis, the patients were divided into several relatively homogeneous groups. For each group estimates were made of the proportions who, at

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specified intervals had had a subsequent hemorrhage, had died from hemorrhage or other ulcer complication, had had a subsequent operation for peptic ulcer

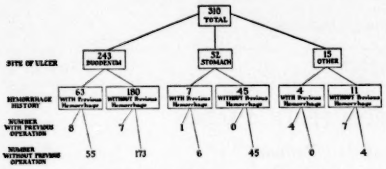

FIGURE 1. *Diagnosis and History of 310 Patients with Acute Hemorrhage from Peptic Ulceration.*

and had died from causes not connected with ulcer. The proportions were estimated by a life-table procedure similar to that set forth by Berkson and Gage[6] and Merrell and Shulman.[7]

RESULTS

Of the 310 patients, 292 (94.2 per cent) were satisfactorily followed. Of the 18 not satisfactorily followed, 9 were not traced beyond their discharges from the University Hospitals after recovery from their index hemorrhages. The remaining 9 were traced for varying periods, but the number and dates of subsequent hemorrhages and operations and their status as of July 1, 1951, were not ascertained. Some information about each of the 18 is known and utilized. For instance, all 18 survived the index hemorrhage, and 1 was followed satisfactorily for fourteen years.

Duodenal Ulcer

There were 173 patients with duodenal ulcer in whom no hemorrhage or operation had occurred before the index hemorrhage. This was the largest subgroup with a uniform history and diagnosis and was therefore the largest subgroup from which interpretable information about the subsequent course of events could be obtained. Figure 2 presents schematically the subsequent course of events (hemorrhages, operations and deaths) in those 173 patients

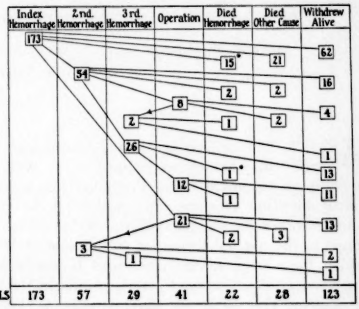

FIGURE 2. *Fate of 173 Patients after One Initial Hemorrhage from Duodenal Ulcer.*

**Two patients died of ulcer complication other than hemorrhage, fifty-four months after the index hemorrhage and thirty-five months after a third hemorrhage, respectively.*

up to July 1, 1951, or the last date of observation for those not satisfactorily followed. On this date 62 patients were alive and had had no further hemorrhages or operations. The intervals between the index hemorrhage and the last date of observation in these 62 cases are shown in the third column of Table 1; the other columns give lengths of time from the index hemorrhage to subsequent hemorrhage, operation or death, whichever occurred first, in the remaining cases. Since all patients were not observed

TABLE 1. *Time of Occurrence of First Events for Patients* with Duodenal Ulcer and No Previous Hemorrhage or Operation.*

INTERVAL AFTER INDEX HEMORRHAGE	SURVIVORS WITHOUT HEMORRHAGE OR OPERATION AT START OF PERIOD	PATIENTS WHO WITHDREW FROM STUDY†	PATIENTS WITH FURTHER HEMORRHAGE	PATIENTS WHO UNDERWENT OPERATION	PATIENTS WHO DIED FROM HEMORRHAGE	PATIENTS WHO DIED FROM OTHER CAUSES
mo.						
0-1	173	5	1	11	14	0
2-35	142	8	31	4	0	9
36-59	90	12	8	2	1	5
60-83	62	15	5	2	0	3
84-119	37	7	5	2	0	2
120 & over	21	15	4	0	0	2
Totals	—	62	54	21	15	21

*Each patient listed only once & only under 1st event.

†7 patients not traced; remainder alive without subsequent hemorrhages or operations on closing date of study.

Figure 1 shows the distribution of patients according to the sites of their ulcers and for each site the number who had had previous operations and hemorrhages. On their entries 243 patients had duodenal ulcers, and 52 had gastric ulcers; in the other 15 the ulcer was anastomotic or multiple, or the site could not be certainly identified.

for the same length of time and therefore were not equally exposed to the risk of subsequent hemorrhage, the lengths of time they were exposed were analyzed by a life-table method; this method, here, estimates what proportion of the patients would have had a subsequent hemorrhage within a certain period if all had been exposed for that period.

Table 2 shows the risk of further events by time after the index hemorrhage. Among the patients who recovered from the index hemorrhage without surgical intervention it was estimated that the risk of dying or having another hemorrhage or having an operation within five years was 45 per cent. This risk can be thought of as a composite of the risks of having a subsequent hemorrhage, of death and of operation and can be measured directly. The component risks are not all subject to direct evaluation

TABLE 2. *Risk of Having Subsequent Hemorrhage, Undergoing Operation or Dying (from Any Cause) after Recovery from Index Hemorrhage Due to Duodenal Ulcer.*

AGE	NO. OF PATIENTS	RISK AFTER 2 MO.	RISK AFTER 3 YR.	RISK AFTER 5 YR.	RISK AFTER 7 YR.	RISK AFTER 10 YR.
yr.		%	%	%	%	%
Under 50	103	1	29	37	50	64
50 & over	70	0	37	57	62	70
All ages	173	1	32	45	55	67

because the other risks are always present. For example, one cannot evaluate directly the risk of having a subsequent hemorrhage within five years by dividing the number of patients who had a hemorrhage within five years of the index hemorrhage by the number who survived the index hemorrhage, because some died before having been

TABLE 3. *Fate of Patients with Duodenal Ulcer without Hemorrhage or Operation before Index Hemorrhage and Continued under Medical Management after Survival of Index Hemorrhage.*

RISK	INTERVAL AFTER INDEX HEMORRHAGE				
	2 MO.	3 YR.	5 YR.	7 YR.	10 YR.
	%	%	%	%	%
Subsequent hemorrhage	1	24	31	37	48
Death from subsequent hemorrhage	0	1	3	3	7
Death from cause unrelated to hemorrhage	0	7	13	18	21

exposed for a full five years to the risk of having a subsequent hemorrhage. The concept of component risks, even if they are evaluated indirectly, is useful in the study of disease.

In Table 3 the chances of having a subsequent hemorrhage, dying from a subsequent hemorrhage and dying from a cause independent of ulcer are considered at intervals up to ten years after the index hemorrhage in the 173 patients who were continued under medical management after recovery from the index hemorrhage. (The term "medical management" indicates management other than surgical and does not necessarily mean that the patients were continuously under rigid dietary and medication control.) When any patient among them was operated upon, the remainder of his course after operation was not included in this analysis. The interpretation to be given to these figures is that within the five years of their first hemorrhage:

TABLE 4. *Race and Sex of Patients with Duodenal Ulcer.*

SEX	RACE		TOTALS
	WHITE PATIENTS	NEGRO PATIENTS	
Male	112	23	135
Female	23	15	38
Totals	135	38	173

Of 100 patients with duodenal ulcer who survived a first hemorrhage, if they were not operated upon and did not die of other causes first, 31 would have had at least one subsequent hemorrhage, and 69 would not have had any subsequent hemorrhages (these figures were not observed directly because all patients were not observed for five years, all did not survive the index hemor-

TABLE 5. *Age of Patients with Duodenal Ulcer at Time of Index Hemorrhage.*

AGE	NO. OF PATIENTS
yr.	
10-19	2
20-29	19
30-39	30
40-49	52
50-59	28
60-69	27
70-79	13
80-89	2
All ages	173

rhage, some did undergo operation and some did die of other causes, but these figures are life-table estimates of the component risks).

Of 100 patients who survived the first hemorrhage, if they were not operated upon and did not die of other causes, 3 would have died of a subsequent hemorrhage (or other ulcer complication).

Of 100 patients who survived the first hemorrhage, if they were not operated upon and did not die of a subsequent hemorrhage, 13 would have died of unrelated causes (some may have had subsequent hemorrhages).

Within this study, there were various subgroups for which corresponding rates could be computed. Thus, an idea may be obtained of how such factors

as age and number of hemorrhages altered this prognosis.

The race and sex distribution of the 173 patients with duodenal ulcer who had had no previous hemorrhages or operations is presented in Table 4. Since the subsequent hemorrhage and mortality did not apparently differ by race and sex, they are not distinguished in the rates presented.

The age distribution (at time of index hemorrhage) of the 173 patients is presented in Table 5. For analysis, the 103 under age fifty were placed in one group, and the remaining 70 in the other group.

TABLE 6. *Risk of Subsequent Hemorrhage under Continued Medical Management, According to Age at Time of Index Hemorrhage.*

AGE	NO. OF PATIENTS	RISK 2 MO. AFTER INDEX HEMORRHAGE	RISK 3 YR. AFTER INDEX HEMORRHAGE	RISK 5 YR. AFTER INDEX HEMORRHAGE	RISK 7 YR. AFTER INDEX HEMORRHAGE	RISK 10 YR. AFTER INDEX HEMORRHAGE
yr.		%	%	%	%	%
Under 50	103	1	25	29	37	49
50 & over	70	0	22	35	39	45
All ages	173	1	24	31	37	48

TABLE 7. *Mortality from Index Hemorrhage Due to Duodenal Ulcer, According to Age.*

AGE	NO. OF PATIENTS	NO. OF DEATHS	MORTALITY
yr.			%
Under 50	103	6	5.8
50 & over	70	10	14.3
All ages	173	16	9.2

Table 6 presents the chances that the older and the younger groups had for undergoing a subsequent hemorrhage while under continued medical management. These chances were approximately equal for the two age groups throughout the first ten years after the index hemorrhage.

TABLE 8. *Risk of Death from Subsequent Hemorrhage under Continued Medical Management, According to Age at Time of Index Hemorrhage.*

AGE	NO. OF PATIENTS	RISK AFTER 2 MO.	RISK AFTER 3 YR.	RISK AFTER 5 YR.	RISK AFTER 7 YR.	RISK AFTER 10 YR.
yr.		%	%	%	%	%
Under 50	103	0	0	2	2	2
50 & over	70	0	4	4	4	15
All ages	173	0	1	3	3	7

The influence of age on the mortality from the index hemorrhage is shown in Table 7 and that on mortality from hemorrhages after the index in Table 8. The risk of dying from the first hemorrhage was markedly higher for older people than for younger. The risk of dying from subsequent hemorrhages was quite similar in the two age groups up to seven years after the index hemorrhage and thereafter was apparently greater for the older persons, but that difference represents two observed deaths and is statistically nonsignificant.

The survivors' chances of undergoing operation for peptic ulcer are presented in Table 9 for the two age groups. These figures are difficult to interpret because of the many physicians, surgeons and operation procedures involved, but are presented to give a more complete description of the events occurring in the cases observed. Up to three years after the index hemorrhages the chances of undergoing operation were about the same in the two groups; after three years there were no first operations among the older patients.

TABLE 9. *Risk of Undergoing Operation for Patients with Peptic Ulcer after Index Hemorrhage Due to Duodenal Ulcer, According to Age at Time of Index Hemorrhage.*

AGE	NO. OF PATIENTS	RISK 2 MO.	RISK AFTER 3 YR.	RISK AFTER 5 YR.	RISK AFTER 7 YR.	RISK AFTER 10 YR.
yr.		%	%	%	%	%
Under 50	103	8	14	23	31	40
50 & over	70	6	13	13	13	13
All ages	173	7	14	20	25	32

Table 10 indicates that the chance of having another hemorrhage was much greater after two than after one, but the chance of dying from any one hemorrhage was not significantly greater than that from the others (Tables 11 and 12). Variation in severity of hemorrhages has not been taken into account. Although nearly 90 per cent of the subsequent hemorrhages were confirmed by a hospital or physician's laboratory record, this does not mean that the second hemorrhages were as severe as the index ones.

Table 13 compares the chances of dying from causes unassociated with duodenal ulcer in these 173 persons to the expected proportion dying among a hypothetical group with the same age, race and sex composition, followed for the same lengths of time according to the 1939-1941 life tables.[6,9] The negligible difference suggests that a hemorrhage from duodenal ulcer did not make these patients more susceptible to dying from causes unrelated to ulcer.

Gastric Ulcer

Among the 310 patients in the study 52 had gastric ulcer at the time of the index hemorrhage; 45 of these had had no previous hemorrhages or operations (Fig. 1). Only 28 patients survived the index hemorrhage (Table 14), and a substantial number of them were operated upon at the time of the index hemorrhage or later. Only 11 patients were continued under medical management, and 3 of these had subsequent hemorrhages. This group of patients was too small for reliable estimates of the rates of occurrence of subsequent events.

with a first hemorrhage due to duodenal ulcer to present themselves at University Hospitals. For this reason little attempt has been made to interpret the figures obtained in this study absolutely, and no attempt has been made to compare them with other figures quoted in the past. Within this study, however, morbidity and mortality figures are presented for various subgroups. From comparisons of these, hypotheses may be made concerning how the prognosis was affected by various factors.

TABLE 10. *Risk of Having Another Hemorrhage after Index Hemorrhage and after a First Subsequent Hemorrhage.*

Period under Consideration	No. of Patients	Risk 2 Mo. after Index Hemorrhage	Risk 3 Yr. after Index Hemorrhage	Risk 5 Yr. after Index Hemorrhage	Risk 7 Yr. after Index Hemorrhage	Risk 10 Yr. after Index Hemorrhage
		%	%	%	%	%
After index hemorrhage	173	1	24	31	37	48
After 1st subsequent hemorrhage	54	0	54	64	69	69

TABLE 11. *Risk of Dying from Further Hemorrhage after One and Two Hemorrhages.*

Period under Consideration	No. of Patients	Risk 2 Mo. after Index Hemorrhage	Risk 3 Yr. after Index Hemorrhage	Risk 5 Yr. after Index Hemorrhage	Risk 7 Yr. after Index Hemorrhage	Risk 10 Yr. after Index Hemorrhage
		%	%	%	%	%
After index hemorrhage	173	0	1	3	3	7
After 1st subsequent hemorrhage	54	0	0	6	6	6

TABLE 12. *Mortality of Index and Subsequent Hemorrhages.*

Hemorrhage No.	Total Patients	Deaths	Mortality %
1	173	16	0.092
2	57	2	0.035
3	29	2	0.069
4	12	0	—
5	2	0	—
6	1	0	—

Data from the patients with duodenal ulcer indicate that a patient had chances of about 1 out of 3 of having a second hemorrhage within five years of his first one, if he lived and no operations were performed. The chances were 2 out of 3, however, that he would have a third hemorrhage within five years after his second (Table 10). The chances of having these repeated hemorrhages, however, do not appear to have been affected by the age of the patient. The mortality risk of subsequent hemorrhages did not seem to be much different from that of the index hemorrhages, but the mortality from index hemorrhages, and possibly from succeeding bleeding episodes as well, was higher in older than in younger persons. It appears that the patient with the poorest prognosis was the one who had had at least two bleeding episodes (because of the increased likelihood of subsequent hemorrhages) and was over fifty

TABLE 13. *Risk of Death from Causes Not Connected with Duodenal Ulcer.*

Group under Study	No. of Patients	Risk 2 Mo. after Index Hemorrhage	Risk 3 Yr. after Index Hemorrhage	Risk 5 Yr. after Index Hemorrhage	Risk 7 Yr. after Index Hemorrhage	Risk 10 Yr. after Index Hemorrhage
		%	%	%	%	%
All cases	173	0	7	13	18	21
1939-41 life tables*			6	10	15	22

*Expected mortality from U. S. life tables, 1939-41, for comparison.

Discussion

It would be difficult to make conjectures about all the factors of selection that caused the 173 patients

years of age (because of increased risk for older persons of dying from individual hemorrhages).

Summary

Of 310 patients who had one or more episodes of acute bleeding due to peptic ulcer at University Hospitals between 1936 and 1948, 94.2 per cent were followed until July 1, 1951, for information about subsequent acute hemorrhage, death from subsequent acute hemorrhage or other ulcer complication, and death from causes unrelated to ulcer.

Of the 173 patients whose index hemorrhages were due to duodenal ulcer and who had had no hemorrhages or operations before the index hemorrhage, those patients who survived the index hemorrhage and were continued under medical management had a 31 per cent chance of having a second hemorrhage within five years of the first; those who survived a second hemorrhage and were continued under medical management had a 64 per cent chance of having a third hemorrhage within five years of the second.

The age of the patient did not influence the chance of having a second hemorrhage from duodenal ulcer, but the mortality from the initial hemorrhage, and probably from subsequent hemorrhages, increased with age.

Survival from a massive hemorrhage from duodenal ulcer did not appear to alter the risk of later death from causes other than ulcer.

The patient with duodenal ulcer who had had multiple acute hemorrhages and was over fifty years of age offered the least favorable prognosis for continued successful medical management.

The mortality from the initial hemorrhage from gastric ulcer was markedly higher in patients over fifty years of age than in younger patients.

TABLE 14. *Mortality from Index Hemorrhage Due to Gastric Ulcer, According to Age.*

AGE	NO. OF PATIENTS	NO. OF DEATHS	MORTALITY
yr.			%
Under 50	18	4	22
Over 50	27	13	48
Totals	45	17	
Average			38

We are indebted to Mrs. Grace Achtermann and Mrs. Dorothy Schulz for aid in tracing these patients.

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COLLAGEN DISEASE OF THE SMALL BOWEL*

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IT is the purpose of this paper to discuss collagen disease of the small bowel and to report this condition in its early and late stages so that it can be readily recognized clinically in the operating room and possibly treated earlier. It is suggested that this lesion has not been reported by surgeons for lack of such a description and that it is more common than has been suspected. It was the primary lesion that necessitated operation in 3 cases reported below.

The term collagen disease implies a systemic alteration of the connective tissue as seen in rheumatic fever, lupus erythematosus disseminatus, generalized scleroderma, dermatomyositis, serum sickness, periarteritis nodosa[1] and possibly intestinal lipodystrophy (Whipple's disease).[2] Although the cause of collagen disease is still undetermined, much has been learned about the chemical nature of the ground substance and fibers constituting the collagen, with the aid of the electron microscope and the polarimeter.[3] Mucopolysaccharides, notably hyaluronic acid and chondroitin sulfuric acid in different degrees of polymerization,[4] have been shown to be present in connective tissue.

The Ritter–Oleson periodic acid technic was used in the cases reported below, as well as the Gömöri, hematoxylin and eosin and trichrom Mallory stains, though the last two common technics are sufficient.

Involvement of the gastrointestinal tract with collagen disease has often been described in the esophagus. Descriptions of gastrointestinal-tract involvement beyond the esophagus have been infrequent. Kraus[5] (1924) seems to have made first report of

*Presented at a meeting of the Philadelphia Academy of Surgery, January 6, 1956.

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small-intestine changes, followed by Rake[6] (1931), Bevans[7] (1944), Hale and Schatzki[8] (1944), Goetz[9] (1945), Lushbaugh et al.[10] (1948), a case reported in 1950,[11] Prowse[12] (1951), Pugh, Kvale and Margulis[13] (1951), Abrams, Carnes and Eaton[14] (1954) and Leinwand et al.[15] (1954). In these reports lesions of the gastrointestinal tract were reported at autopsy[5-7,10,12,13] or were discovered on gastrointestinal series in known cases of scleroderma.[8,9]

Case Reports

Case 1.* S.H. (J.C.M.C. 008540), a 47-year-old single male laborer, was first seen on January 16, 1952, for the chief complaint of pain in the upper abdomen, anorexia, occasional vomiting and a weight loss of 10.4 kg. (23 pounds) in the preceding 6 months. The pain was dull and burning, occurring practically every day, usually about an hour after meals and relieved by bicarbonate. Bowel movements were regular. Physical examination was not remarkable except for evidence of weight loss. The weight was 63.5 kg. (140 pounds). The abdomen revealed no tenderness, distention or masses.

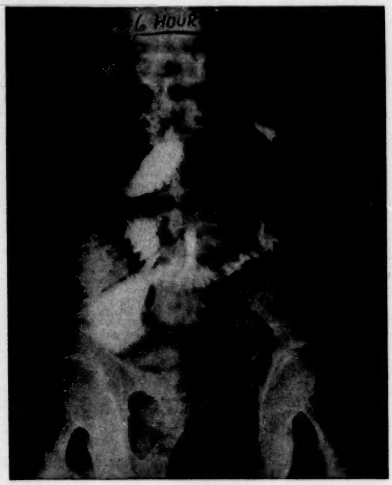

Figure 1. *Barium-Swallow Study in Case 1.*
At six hours, the stomach has emptied, but a residue of barium is still present in the proximal portion of the duodenum and proximal jejunum.

A gastrointestinal study by means of a barium meal revealed a normal esophagus, stomach and duodenal bulb. There was dilatation of the 2d part of the duodenum and also of the proximal portion of the 3d part. There was an apparent narrowing just proximal to the ligament of Treitz, and no barium passed beyond this point in a period of 10 minutes. After 1 hour pooling of the barium was again noted in the proximal jejunum, which appeared somewhat dilated. At 6 hours (Fig. 1) the stomach had emptied, but a residue of barium was still present in the proximal portion of the duodenal sac. A diagnosis of probable neoplasm of the 3d portion of the duodenum was made, and the patient was admitted to the Jersey City Medical Center on February 18.

*Referred by Dr. Leonard Troast, Jersey City, New Jersey.

The temperature was normal and the physical examination was unchanged except that shortly before operation the anesthetist called attention to bluish discoloration of the extremities. Further questioning brought out the extreme sensitivity to cold, thus first calling attention to the quadrilateral Raynaud's syndrome. At operation the skin was cut with difficulty, but the significance of scleroderma was not appreciated until 2 years later.

Figure 2. *Section of the Small Bowel in Case 1, Showing Marked Sclerosis of the Connective Tissue of the Serosa, with Atrophy and Partial Replacement of the Muscular Coat by Collagenous Fibrous Tissue (X75).*
The vessels are not severely involved.

Urinalysis was negative. Examination of the blood revealed a red-cell count of 5,000,000 to 6,000,000, with a hemoglobin of 16.5 gm. per 100 ml., and a white-cell count of 10,450, with a normal differential. The nonprotein nitrogen was 30 mg., and the blood sugar 97 mg. per 100 ml.

The 1st exploratory laparotomy was performed on February 25. Starting just proximal to the ligament of Treitz and extending some 90 cm. distally, the jejunum was edematous, flabby, distended to about twice its normal caliber and violaceous. The regional lymph nodes in the mesentery were enlarged and soft. The lymphatics radiating from nodes to the bowel were outlined by engorgement with a white substance. Peristalsis was diminished in this area. It was thought that this was a form of regional enteritis limited to the jejunum. The decision was made to do no definitive surgery at this time, but to close the abdomen and hope for a remission. Histologic diagnosis of a lymph node excised for biopsy was chronic lymphadenitis. After an uneventful postoperative course, the patient became asymptomatic and was discharged on March 15. About 5 days after leaving the hospital abdominal cramps, distention and a mild diarrhea, consisting of 3 loose watery, nonbloody stools a day developed for the 1st time. On March 29, examination of the abdomen demonstrated marked distention and hyperactive bowel sounds. On April 1, barium-meal study again showed dilatation of the proximal duodenum, with delay in passage of the barium meal into the jejunum. Serial films revealed dilated loops of jejunum, with alteration of the mucosal pattern. The patient was

deal of melanin. The corium is crowded with thick, rigid collagen fibers. The papillae contain dense masses of fine collagen fibers. The subcutaneous tissue shows extensive fibrosis, with both thick and thin collagen fibers, especially around the blood vessels and nerves. Both corium and subcutaneous tissues are rich in ground substance. The arteries reveal marked fibrosis of the intima

FIGURE 7. *Section of the Intestine in Case 2, Showing a Vein Infiltrated by Collagen Deposits in All Layers (X150).*

and media (Fig. 5). The veins show heavy deposits of collagen in all layers (Fig. 6). The basement membrane of small vessels is thickened. Both the veins and the nerves contain an unusually large amount of ground substance. The subcutaneous fat tissue is markedly atrophic and infiltrated with histiocytes laden with iron pigment.

Only one section of small intestine is available. The presence of suture material indicates that it came from an operative site. The mucosa of this specimen is narrow and edematous. It is separated from the muscular coat by a wide zone of connective tissue containing numerous thick and thin collagen fibers and abundant ground substance. The picture of the arteries and veins is similar to that in the skin (Fig. 7). Some vessels are filled with organized thrombi. Also present are a good many round cells and histiocytes laden with iron pigment. The muscular coat is greatly atrophic in places and replaced by fibrous tissue containing many collagen fibers (Fig. 8). The suture material is surrounded by leukocytes and macrophages.

No clinical signs of scleroderma were observed in this case though the microscopical appearance with Ritter–Oleson periodic acid stain revealed generalized scleroderma involving the skin, esophagus, small intestine, lung, kidneys and heart and even the pancreas, liver, spleen and bone marrow. The true nature of the diagnosis was not established until postmortem examination. X-ray studies of the gastrointestinal tract showed the typical dilated bowel with barium retention and diminished peristalsis. The free air under the diaphragm has not been seen in other cases. The gross description of the gastrointestinal tract, characterized by the gray areas and the enlarged regional mesenteric lymph nodes, is typical of the late stage corresponding to advanced polymerization of the mucopolysaccharides.

CASE 3.* F.S. (J.C.M.C. 018373), a 23-year-old longshoreman, was admitted to Jersey City Medical Center for the 1st time on October 28, 1954, complaining of epigastric pain of 1 year's duration. The pain came on 5 to 10 minutes after eating and was usually associated with marked left-upper-quadrant distention and radiation to the left side of the chest posteriorly. The patient had recently lost 4.5 kg. (10 pounds) in weight. Nausea was present, but no vomiting.

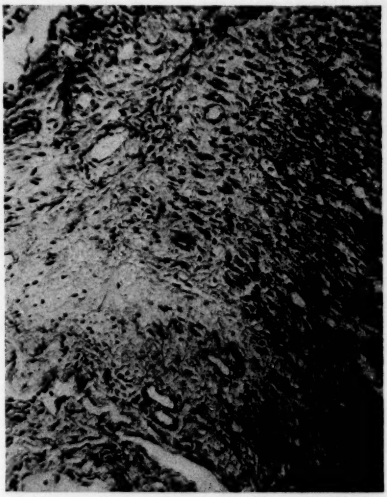

FIGURE 8. *Section of the Intestine in Case 2 (X150). The muscular coat is atrophic in places and replaced by tissue.*

Physical examination revealed diffuse tenderness at the mid-epigastrium, with slight guarding. A gastrointestinal series taken shortly before admission showed normal mucosal markings. There was no barium retention. Barium-enema examination in the hospital on November 5 was not diagnostic.

Exploratory laparotomy was undertaken on November 8. The peritoneum contained some excess free fluid (less than 500 ml.). The peritoneum was edematous and moist. The stomach wall was thickened and pink, with engorgement, and edematous. Gastrotomy was done to palpate the duodenal mucosa. No ulcer was present. The pylorus was patent. The stomach wall was thickened and appeared to have lost elasticity and normal peristalsis. The duodenal wall was similarly affected. The omentum was also thickened, contracted and adherent to the colon and stomach. Division of the omentum and dissection of the adherent posterior gastric wall from the pancreas showed the pancreas to have become pink and rubbery. Starting at the ligament of Treitz, the jejunum for a distance of about 90 cm. was also pink, distended to 1½ times the normal

*Referred by Dr. Sam Kraemer, of Jersey City, New Jersey.

size and macerated. The mesentery was thickened and contained lymphatics distended with white material leading to the regional lymph nodes, which were markedly enlarged. Figure 9 shows the appearance of this particular feature, which is believed to be of diagnostic significance in the early state.

A lymph node and full-thickness circumference wedge of jejunum were excised for biopsy. No definitive surgery was done at this point since it was impossible to get beyond the limits of involved viscera.

Histologic studies were reported as follows:

The small intestine is covered with a well preserved mucosa. The underlying submucosa shows abundant, thick collagen fibers. No muscularis is present. The vessels contained in the submucosa are not materially changed.

The pieces of mesentery contain an area of dense fibrosis, which is crowded with thick collagen fibers. In the midst of the fibrotic area several well circumscribed lymph follicles are located, but no lymph node is identified.

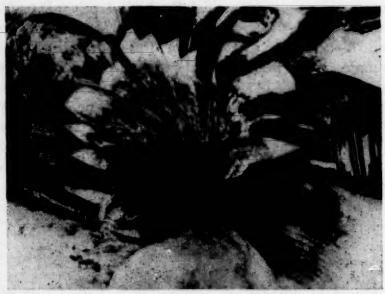

FIGURE 9. *Early Stage of Collagen Disease of the Small Bowel in Case 3, Showing Dilatation and Lymphatics Distended with White Substance Leading into Markedly Enlarged Regional Lymph Nodes.*

This patient had the typical symptoms of pain and distention of the upper abdomen after food ingestion, but x-ray examination and the peripheral signs of scleroderma and Raynaud's phenomena were absent. The appearance at laparotomy and the histologic description established the diagnosis. The patient will require further observation for development of other manifestations of collagen disease.

DISCUSSION

In these cases of collagen disease of the small bowel involvement of the skin or Raynaud's phenomenon was not always present. A characteristic x-ray appearance of the bowel when visualized can be important in preoperative diagnosis, but was absent in Case 3. The gross appearance of the bowel in the early stages of collagen disease, characterized by edema, diminished tone and peristalsis, increased caliber, associated with enlarged, soft lymph nodes and dilated radial lymphatics filled with white substance, provides an added means of gross identification in the absence of other collagen-disease characteristics. This led to the true estimate of the diagnosis in Case 3.

The description of the late stage of collagen disease of the small bowel is characterized by white, sclerosed serosal surfaces, diminished tone and peristalsis, with hard, palpable lymph nodes. Free peritoneal fluid was not seen in any case. The gross appearance of intestinal lipodystrophy (Whipple's disease) is associated with enlarged, soft lymph nodes. The mesentery in these cases also showed massive infiltration of fatty substances. A recent study with the use of mucopolysaccharide stains[2] shows that the "fatty substance," which was supposed to occupy the vacuoles seen on microscopical examination and hitherto offered as a diagnostic characteristic of intestinal lipodystrophy, is really ground substance that constitutes collagen. Thus, intestinal lipodystrophy may be another form of collagen disease of the small bowel.

The microscopical characteristics, in which collagen has replaced the muscularis and has infiltrated the subserosal and submucosal spaces of the bowel, offer the final criterion. In other organs, such as the heart, kidney and spleen and even bone, sclerosis is shown, as represented in the autopsy specimens in Case 2.

SUMMARY AND CONCLUSIONS

Three cases of collagen disease, primarily of the small bowel but also of other areas, are presented. The characteristics of the clinical picture and x-ray studies are described.

The gross appearance of the bowel in the early stages of the disease and in the terminal stages are presented so that the true diagnosis may be suspected.

The microscopical appearance is the final criterion in diagnosis.

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SERUM ENZYMES*

I. Serum Lactic Dehydrogenase in Myocardial Infarction

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SAN FRANCISCO

RECENTLY, the determination of serum levels of glutamic oxalacetic transaminase was introduced as an aid in the differentiation of myocardial infarction and pulmonary infarction or embolism.[1-4] This test is based on the knowledge that heart muscle is rich in transaminase and on the assumption that necrosis of the muscle liberates significant amounts of the enzyme into the blood, where it can be measured. From the data reported the assumption appears justified. However, three main drawbacks to this method exist: abnormal serum levels of transaminase persist only twenty-four to seventy-two hours after the infarction occurs; some patients with unquestioned infarcts of limited extent do not have abnormal serum levels of the enzyme; and the method is technically quite laborious. A simplified technic has been suggested more recently[5] that may alleviate the technical rigors but cannot obviate the first two difficulties.

It is obvious that heart muscle is not limited in its enzyme content to transaminase but is also rich in many other enzymes, particularly those concerned with glycolysis. What appears to apply to transaminase in necrotic muscle should also apply to these other enzymes. This has been found to be so, and the present report is concerned with evidence that serum levels of lactic dehydrogenase are of great help in the diagnosis of myocardial infarction. Data are presented comparing serum levels of glutamic oxalacetic transaminase, lactic dehydrogenase, aldolase and hexose isomerase in 50 patients in whom the diagnosis of myocardial infarction was entertained.

CLINICAL MATERIAL

The patients have been divided into several groups. Group A consisted of 24 patients in whom a clinical diagnosis of recent (within one week) myocardial infarction had been made by the usual clinical means or autopsy or both. Group B comprised 7 patients in whom such a diagnosis of infarction of more than a week's duration had been made by clinical methods. Group C, 19 patients, consisted of patients in whom an initial question of myocardial infarction had been answered in the negative and in whom other causes for their complaints had been established. In this group most of the patients had classic angina pectoris.

Data are presented on 10 other patients with the following diagnoses: hepatitis (3 cases), nephritis (3 cases), dermatomyositis (2 cases) and cerebrovascular accident (2 cases).

METHODS

Of the utmost importance for these determinations is the technic of collecting and preparing blood samples. The slightest degree of hemolysis in a specimen can result in artificially high levels of transaminase and the glycolytic enzymes in serum, since red blood cells are rich in these materials. All samples were taken with the utmost care to avoid hemolysis, and blood was allowed to clot at room temperature and the clot to retract. The blood was then centrifuged at 2000 r.p.m. for thirty minutes. The serum was harvested and re-centrifuged. The second centrifugation was necessary to clear the serum of red cells.

The technics used for enzyme analysis were those described by others, with some minor variations.[1,6-8]

Transaminase

Glutamic oxalacetic transaminase (GOT) is an enzyme that catalyzes the transfer of an amino group from the alpha position of aspartic acid to alpha ketoglutaric acid, with the formation of glutamic acid and oxalacetic acid. In the presence of malic dehydrogenase and reduced diphosphopyridine nucleotide (DPNH) oxalacetic acid is reduced to malic acid and DPNH is oxidized to DPN; this reaction is accompanied by a decrease in optical density at 340 millimicrons in the spectrophotometer, and is used in the assay of Karmen et al.[1] In this laboratory the average normal value was 21 units per milliliter of serum per minute. Normal subjects showed values up to 31 units per milliliter per minute, and for the purposes of this report the upper limit of normal was taken as 32 units per milliliter of serum per minute.

Lactic Dehydrogenase

Lactic dehydrogenase (LDH) is an enzyme that catalyzes the reversible reaction:

$$\text{Pyruvic acid} + \text{DPNH} \rightleftharpoons \text{lactic acid} + \text{DPN}.$$

The equilibrium of the reaction greatly favors lactate formation, and therefore pyruvate and DPNH were used as the substrates.[9] Other methods exist for measuring the same enzyme using lactate and DPN.[10] These seem equally simple but perhaps less ideal.

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The reaction is carried out in phosphate buffer at pH 7.8. The reaction mixture of Hill and Levi[6] was modified, bicarbonate being omitted. Each day the following reaction mixture was prepared from reagents that had been kept at −10°C.:

26.0 ml. of 0.1-molar phosphate buffer, pH 7.8,
1.0 ml. of 0.01-molar sodium pyruvate in PO_4 buffer, pH 7.8,
3.0 ml. of DPNH, 1.0 mg. per milliliter in distilled water;

TABLE 1. *Results in Group A (Patients with Recent Myocardial Infarction).*

PATIENT	SERUM GOT	SERUM LDH	SERUM ALDOLASE	SERUM HEXOSE ISOMERASE
	units/ml./ min.	*units/ 0.01 ml.*	*units/ml.*	*units/ 0.04 ml.*
Tali	390.0	795	50.0	690
VanB	10.0	214	8.8	55
Gene	21.0	147	7.9	
Wolf	134.0	270	34.0	338
LaGa	185.0	324	26.0	144
Henn	92.0	496	12.8	45
McVa	13.0	115	10.4	84
McGo	15.0	180		
Geor	18.0	190		
Roch	100.0	120		
Arsa	23.0	227		
Open	31.0	152	7.2	36
Lewi	46.0	309	15.6	56
Forb	475.0		14.7	111
Flet	48.5	254		
Syve	55.0	285		
Stic	27.5			
Nich	12.5	162	4.2	28
Ehrm	62.0	213	6.5	56
Edwa	40.5	162	14.4	
Chan	20.0	144	10.1	
Holc	215.0	348	58.4	
Kuhl	24.0	118	9.8	76
Cumm	15.0	144	8.7	70
Normal value	<32.0	<110	<9.0	<40

3.0 ml. of the reaction mixture was added to each cuvette. A control cuvette was set up by the addition of 0.1 ml. of water. To each of the other cuvettes 0.1 ml. of diluted serum was added. Serum was diluted 1:10 in distilled water just before the determinations were carried out. When the activity was extremely high further dilution was necessary. All measurements were carried out in a Beckman DU Spectrophotometer at a wave-length setting of 340 millimicrons. After mixing of serum and reagents, the control cuvette was used to set the spectrophotometer at an optical density of 0.500 by use of the slit-width control. The optical density of the unknowns was then recorded. All cuvettes were then incubated at 38°C. for thirty minutes. After incubation the control was again set at 0.500, and the optical density of the unknowns recorded. The change in optical density of the unknowns was taken as the LDH activity of 0.01 ml. of serum and expressed as units per 0.01 ml. When correction for further dilution was necessary this was carried out.

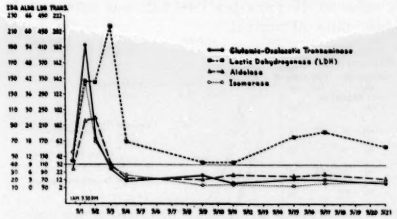

FIGURE 1. *Levels of Various Enzymes in LaGa, a Fifty-two-Year-Old Man with Classic Myocardial Infarction. This patient was in shock for two days and received norepinephrine. GOT, aldolase and isomerase were normal on the second day. LDH was still elevated on the eighth day, with a later rise that is unexplained. Recovery was excellent.*

In this laboratory normal values averaged 90 units per 0.01 ml. of serum. In no case was the value greater than 110 units, and this figure was taken as the upper limit of normal.

Aldolase

This enzyme catalyzes the splitting of fructose-1,6-diphosphate to d-glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. This assay was run exactly as described by Sibley and Lehninger.[7] The modifications suggested by Beck[11] seem of value, but in this laboratory the present method has had satisfactory results in more than 1500 determinations over an eighteen-month period. Results have also been compared with those obtained with the spectrophotometric method of Warburg, and comparable values obtained.[12,13] Results were expressed in units per milliliter of serum. A unit is the amount of enzyme that will split 1.0 cu. mm. of fructose-1,6-diphosphate in one hour under the conditions of the test. Normal values in this laboratory averaged 5.0 units per milliliter of serum with a range of 2.5-8.5 units per milliliter. Values over 9.0 units per milliliter were taken as abnormal.

Hexose Isomerase

This enzyme catalyzes the reaction:

Glucose-6-phosphate ⇌ fructose-6-phosphate.

In the method of Bodansky[8] color developed by fructose-6-phosphate in the presence of alcoholic

resorcinol and hydrochloric acid is used to measure enzyme activity. Bodansky's method was followed, except that concentrated hydrochloric acid was used in place of 10.0 normal hydrochloric acid for color development. Results obtained were in micrograms of fructose-6-phosphate per 0.04 ml. of serum. By use of a chart prepared by Bodansky these values were converted to units per 0.04 ml. of serum. Average values in normal subjects were 25 units per 0.04 ml., with a range of 8 to 38 units per 0.04 ml. A value of 40 units per 0.04 ml. was taken as the upper limit of normal.

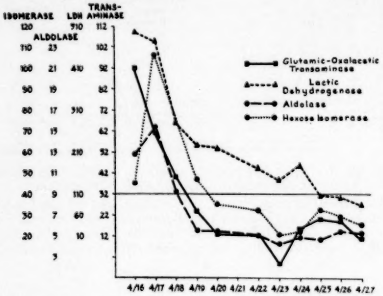

FIGURE 2. *Levels in Ssy, a Fifty-five-Year-Old Man. This patient had an uneventful course after a moderately severe myocardial infarction. Transaminase and aldolase were normal on the third day after infarction, hexose isomerase was normal on the fourth day, and LDH remained abnormal until the ninth day.*

RESULTS

Of 24 patients with recent myocardial infarction the measurement of serum levels of the various enzymes revealed elevated values in all but 1 (Table 1). GOT levels were abnormal in 12 of the 24. It is worth noting that in many of these patients blood was not taken for enzyme analysis on the day after the attack, but several days later. The same conditions apply to serum LDH levels, which were measured in 22 of the 24 patients. In each case an abnormally high serum level of LDH was found. In 1 of these the abnormality was minimal.

In 17 patients measurement of serum aldolase was performed, and elevated values were found in 11. Similarly, in 13 patients serum hexose isomerase activity was determined and was found to be abnormal in 10.

One patient (Stic), who had had an undoubted myocardial infarction four days before blood analysis, showed no abnormality of GOT, the only enzyme that was measured.

One other patient (McVa) deserves special mention. This man had a sudden episode of chest pain with rapid recovery. On clinical grounds, including electrocardiograms, it was thought that he had not had a myocardial infarction. Daily determinations of serum enzymes showed an elevation of LDH and hexose isomerase, but not of GOT or aldolase. All values returned to normal in two days. A week later he died from a rupture of an aneurysm of the abdominal aorta. At autopsy a small myocardial infarct of about two weeks' duration was found. The only evidence during life of this condition was an elevation of serum enzyme content.

In 6 patients serial determinations of serum levels of the four enzymes were carried out. Figures 1 and 2 show representative cases; it can be seen that initial abnormalities of serum levels of all the enzymes measured were of short duration, and that return to normal levels of GOT, aldolase and hexose isomerase was quite rapid. Serum levels of LDH persisted at elevated values for a longer period.

One patient (Tali) manifested a striking elevation of the serum levels of each of the enzymes. She was a seventy-two-year-old woman with long-standing diabetes and arteriosclerosis and with a classic and extremely severe myocardial infarction. The values reported in Table 1 were found on the day of the infarct. The peaks reached on the next day were as follows: GOT, 3220 units per milliliter per minute; LDH, 2585 units per 0.01 ml.; aldolase, 296 units per milliliter; and hexose isomerase, 3710 units per 0.04 ml. No evidence of liver or kidney damage was found. The patient died on the fourth day, and no autopsy was performed.

TABLE 2. *Results in Group B (Patients with Myocardial Infarction of More than One Week's Duration).*

PATIENT	SERUM GOT	SERUM LDH	SERUM ALDOLASE	SERUM HEXOSE ISOMERASE
	units/ml./ min.	*units/ 0.01 ml.*	*units/ml.*	*units/ 0.04 ml.*
Wing	21.0	139	6.7	33
Boon	22.5	101		
McQu	23.5	87	4.0	
Grif	13.0	79		29
Andr	18.0	121		
Henn	13.0			
Ayer	9.0	81	6.4	31

In Group B, which included 7 patients with "old" myocardial infarction, abnormalities of serum enzymes were the exception (Table 2). In none of the 7 was an abnormal level of transaminase found. None had high aldolase or isomerase values. Two of 6 had modest elevation of LDH. These results were not surprising in reference to the serial course of serum enzymes demonstrated by Figures 1 and 2.

Group C consisted of 19 patients in whom severe chest pain or arrhythmia had led to a suspicion of myocardial infarction (Table 3). Three of these patients had single enzyme abnormalities of slight de-

gree. In 1 (Gamu) chest pain developed shortly after an abdominal exploration for obstructive jaundice, with deep icterus at the time of examination. It is believed that in this patient the abnormal levels of serum enzymes found may have been related to liver damage. In 3 patients, not included here, surgical operations per se did not affect the serum levels of these enzymes.

One other patient (Morr) had severe pericarditis, with marked ST-segment and T-wave changes in electrocardiograms. High serum levels of LDH were found, but other enzymes were normal.

In the group of patients with miscellaneous illnesses abnormalities of LDH were apparent in each case. In the patients with nephritis this was the only enzyme abnormality detected (Table 4).

TABLE 3. *Results in Group C (Patients without Myocardial Infarction but with Chest Pain or Arrhythmia or Both).*

PATIENT	SERUM GOT	SERUM LDH	SERUM ALDOLASE	SERUM HEXOSE ISOMERASE
	units/ml./ min.	*units/ 0.01 ml.*	*units/ml.*	*units/ 0.04 ml.*
Rixo	16.0	110		
Dunp	20.0	113		
Rudg	27.0			
Hols	15.0	55	7.1	
Broo	21.0	87	4.0	22
Sten		69	3.0	8
Poli	10.0	41	2.5	15
Tjer	19.0	99	4.3	13
Bnee	12.0	101	5.5	28
Stee	15.0	59	6.2	29
Bunn	11.0	61	7.2	20
Howa	18.0	90	3.8	24
Coom	8.0	76	4.1	5
Gamu	35.0	90	15.8	60
Koch	4.5	105	7.0	43
Baco	6.0	107	4.3	24
Rako	10.0	108	3.4	23
Morr	13.0	388	4.3	25
Neyx	17.0	84	11.2	25
Normal value	<32.0	<110	<9.0	<40

Similar elevations of serum enzyme levels were found in 40 per cent of 75 patients with disseminated cancer, and in all but 1 patient in a group of 12 with progressive muscular dystrophy. These results will be presented elsewhere.

DISCUSSION

It is apparent from the data that serum levels of LDH provide a good chemical index of myocardial infarction. No known false-negative results have as yet been found with the LDH determination, and this cannot be said for the GOT values.

After myocardial infarction serum levels of LDH remain elevated for periods considerably longer than those of GOT, aldolase or hexose isomerase. This is of the utmost importance in the diagnosis of myocardial infarction of moderate severity, after which the patient may not consult his physician for several days. In such cases serum GOT levels were rarely abnormal; in each case studied serum LDH was abnormal. One reason for the longer persistence of abnormality of LDH may be that serum levels of LDH rise considerably higher than those of GOT, aldolase or isomerase after tissue damage. If one can assume similar rates of disappearance of each enzyme it would be expected that LDH would be the last to return to normal.

TABLE 4. *Results in Miscellaneous Illnesses.*

PATIENT	SERUM GOT	SERUM LDH	SERUM ALDOLASE	SERUM HEXOSE ISOMERASE
	units/ml./ min.	*units/ 0.01 ml.*	*units/ml.*	*units/ 0.04 ml.*
Nephritis:				
John	29.0	130		21
Ball	20.0	168		
Merr	12.0	117		36
Cerebrovascular accident:				
Goet	10.0	124		
Clar	33.0	175	16.1	80
Hepatitis:				
Barb	163.0	223	52.0	
Char	169.0	302	91.6	
Lind	12.0	164	7.0	
Dermatomyositis:				
Hous	230.0	723	126.0	
Hous	20.0	236	9.0	
Thom	45.0	370	14.9	
Normal value	<32.0	<110	<9.0	<40

The question then arises, How sensitive is the LDH assay as a diagnostic aid? In patient McVa it appeared to be highly sensitive and was, in fact, the only means by which the correct diagnosis was reached. One may postulate that in the absence of other explanations for high serum levels of LDH such an abnormality is evidence of a diagnosis of myocardial infarction. If one can thus make a diagnosis of an infarct, which previously could not have been detected, what is the next step? Should such patients be treated in the same manner as those in whom the diagnosis is achieved by more classical means? These questions must be answered by experience.

In support of the present data is the report by Wacker et al.,[10] who found that serum LDH was

regularly elevated in patients after myocardial infarction. However, Ruegsegger and his associates,[4] in comparing serum levels of transaminase and LDH in dogs with experimental myocardial infarction, were unable to demonstrate any difference in sensitivity of the two methods.

Several abnormalities of serum enzymes were found in patients in Group C, those without myocardial infarction. In most of these patients the abnormality was minimal and no explanation is apparent. Two patients in this group, all the patients in the miscellaneous group (Table 4) and 100 other patients with disseminated cancer or muscle diseases, not included here, form a large group in which abnormalities of serum enzyme levels have been found. Considered strictly from the point of view of myocardial infarction this large number of patients seems to consist of false-positive reactors. This is by no means true. LDH and many other enzymes are widely distributed throughout the body. In addition to the myocardium, skeletal muscle, liver, kidney, brain and many tumors contain considerable amounts of these enzymes. Necrosis of these tissues is presumably no different from necrosis of heart muscle, and liberation of enzymes from necrotic tissue is not dependent on infarction as the causative mechanism. Any cause of tissue destruction, whether it is infection, trauma, infarction or carcinoma, can be associated with abnormal elevation of serum enzyme levels. Pregnancy will also elevate the serum level of LDH.[6]

Like the erythrocyte sedimentation rate, C-reactive protein determination and other nonspecific means of detecting tissue damage, the measurement of serum levels of lactic dehydrogenase, glutamic oxalacetic transaminase, aldolase and hexose isomerase provides nonspecific means of demonstrating tissue breakdown. Serum enzyme levels as presented here seem more sensitive indexes than those previously employed. However, because of nonspecificity, abnormal results must be interpreted with due regard for the clinical situation. If one can exclude other causes for abnormal levels of these serum enzymes such an abnormality may indicate the presence of myocardial infarction.

Summary and Conclusions

The serum level of lactic dehydrogenase (LDH) is an excellent, if nonspecific, index of myocardial infarction. Serum glutamic oxalacetic transaminase (GOT) is, in this laboratory, of little clinical usefulness in this diagnosis, but is of help in the diagnosis of hepatitis.

The superiority of LDH over GOT depends in part on the comparative simplicity of assay of the former and in part upon the greater degree and longer duration of its increase in the serum.

True false-positive values were not demonstrated by any of the enzyme tests. Elevation of serum levels of LDH, GOT, aldolase and hexose isomerase indicated the existence of tissue damage at some site. This site may be the myocardium, but may also be the liver, kidneys, skeletal muscle or brain or may be found in patients with tumors.

It is suggested that by measurement of the serum LDH the diagnosis of myocardial infarction may occasionally be made in cases in which this diagnosis can be achieved by no other means.

I am indebted to Drs. Ben Shenson, Jess Shenson, Claude Callaway, Melvin Black, William Luttgens, Leyland Stevens, Joseph Kriss, Herbert Hultgren, David Rytand and Frank Greenspan and the house physicians of Stanford University and San Francisco City and County hospitals for referring patients and collecting blood samples on the patients included in this report.

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OBSERVATIONS ON THE GLITTER-CELL PHENOMENON*

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THE "glitter cell," a polymorphonuclear leukocyte whose granules show brownian movement, was first described in 1908.[1] As early as 1909 the presence of these cells in urinary sediments was considered evidence of pyelonephritis and against cystitis.[2] In the following years there were occasional descriptions of cells with granular motility in blood and sputum, but it was not until 1949 that the glitter cell, or granular-motility cell, was reintroduced to clinical medicine by Sternheimer and Malbin.[3] These investigators described a supravital stain, compounded of gentian violet and safranine, that facilitated recognition of such cells and of other formed elements in urine. Additional data were presented two years later on the effects of ambient tonicity on the granular motility, whence the cell takes its name. Clinical experiences were described suggesting a correlation between pyelonephritis and the presence of glitter cells in the urine.[4] In 1954 Jackson,[5] using the Sternheimer–Malbin stain, investigated the mechanism of the abnormal staining reaction whereby the nuclear acids of glitter cells took up only the gentian violet in variable amounts, and thus appeared light blue or colorless. This contrasted with the nuclei of other polymorphonuclear leukocytes, which took up both gentian violet and safranine, thus staining an orange-purple shade. The granular motility, as well as the differential nuclear absorption of dye, was considered by this investigator to be the effects of nonspecific injury to cells that decreased cytoplasmic viscosity and allowed brownian movement of the granules. No clinical observations or pathological correlations were made.

The critical need for accurate diagnosis of pyelonephritis has steadily increased with wider recognition of the frequent etiologic role of this disease in hypertension,[6,7] toxemia of pregnancy,[8] chronic renal failure,[9] abdominal-pain patterns[10] and a variety of poorly recognized syndromes.[10] In addition, accurate diagnosis in patients whose renal parenchymal inflammation manifests itself solely by bladder symptoms may be essential to adequate antibiotic therapy.[11] It seems worth while, therefore, to present certain clinical and laboratory observations bearing on the significance of glitter cells in the urine. The supravital stain and the method of staining urinary sediments were those described by Sternheimer and Malbin.[3] The osmolality of various solutions used was determined by the freezing-point method with the apparatus of Bowman et al.[12]

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Laboratory Observations

The staining characteristics of the formed elements of urine are, in general, those described earlier.[3] The nuclei of polymorphonuclear leukocytes stain either orange purple, with no cytoplasmic granular motility, or light blue to colorless, in which case there may be granular motility depending on tonicity of the urine and other factors as discussed below. Nuclei of renal tubular epithelium stain orange, and as described by Sternheimer and Malbin,[3] nuclei of bladder epithelium stain blue, vaginal epithelium purple, hyaline casts pink, red cells faint lavender, and trichomonads light blue. Details of cell morphology and size are also given by these authors. It should be noted that we have occasionally observed glittering (granular motility) in renal tubular cells, trichomonads and large mononuclear histiocytes.

Table 1 shows the staining characteristics and granular motility of polymorphonuclear leukocytes from body fluids other than urine. The figures given are illustrative only of the range of possibilities, for the variation in the same patient is considerable. Typical glitter cells may be found in large amounts in vaginal secretions, with or without trichomonads, and in prostatic fluid, as well as in the aspirate from joints, duodenum and pericardium. The staining reactions of cells from the buffy coat of oxalated venous blood is probably due, as suggested by Jackson,[5] to damage produced by this method of preparation. It is interesting that patients whose urines contain glitter cells do not show an increased percentage of granular motility in cells from their venous blood. Glitter cells from any source retain their granular motility up to several hours at room temperature and may be readily found in urine that has been standing for as long as ninety-six hours.

Table 2 records the effect of suspending granular motility cells, taken from urines of patients with pyelonephritis, in solutions of varying tonicities and then centrifuging for five minutes. The results with glucose, saline solution and normal urine demonstrate inhibition of the brownian movement at concentrations of approximately 600 milliosmols per liter and above. The specific gravities that correspond to this vary widely, depending on the weight as well as the concentration of the solutes. This relation is borne out by the common clinical observation that

granular motility in urines containing heavy molecules such as glucose will continue to be seen at specific gravities over 1.020, whereas in nonglycosuric patients, inhibition is generally apparent at specific gravities around 1.015 or higher. Hypertonic inhibition may be accompanied by nuclear swelling, but all effects are usually reversible by simple dilution. Individual differences among glitter cells are well known, and we have occasionally observed granular motility in urines at concentrations as high as 1030 milliosmols per liter (specific gravity, 1.028). It may be re-emphasized that whereas blue-staining polymorphonuclear leukocytes may or may not glitter, orange-staining cells have never been observed to show granular motility.

TABLE 1. *Glitter Cells in Various Body Fluids.*

SITE OF COLLECTION	NO. OF SPECIMENS EXAMINED	PERCENTAGE OF POLYMORPHONUCLEAR LEUKOCYTES STAINING BLUE	PERCENTAGE OF BLUE-STAINING POLYMORPHONUCLEAR LEUKOCYTES SHOWING GRANULAR MOTILITY
Vagina	6	0-100	50-100
Prostate	2	50	50
Wound drainage	8	20-100	5-100*
Buffy coat of oxalated venous blood	50	100	5-10

*Depending on state of preservation of cells.

Table 2 further demonstrates the failure of normal urine to inhibit granular motility at concentrations under 600 milliosmols per liter. Although Sternheimer and Malbin[4] described an opposite result, they did not state the concentrations of their normal urines, and the discrepancy may be on this basis. It should be noted that plasma, as well as supernatant from glitter-cell urine, does not inhibit granular motility.

Figure 1, which confirms similar observations by Sternheimer and Malbin, strongly suggests the presence in glitter-cell urine of conditions or substances favoring granular motility, independently of total solute concentration. In hypotonic normal urine and saline solution, granular motility could not be induced by the addition of buffy coat from oxalated venous blood and centrifugation for five minutes. On the other hand, the supernatant of glitter-cell urine, added to buffy coat, resulted in widespread and instant glittering. Although cells prepared in this manner are in an unphysiologic and probably injured state, the results indicate sharp differences among various urines and hypotonic solutions in their ability to induce granular motility. It is of great interest that the supernatant from the urine of a pyelonephritic patient shows significantly less ability to induce granular motility if the original specimen has not contained glitter cells.

CLINICAL DISCUSSION

It is clear from the present data, as well as the work of others, that the presence of glitter cells in the urine can in no way be considered a specific reaction to pyelonephritis. Prostatic fluid and vaginal secretions, two common contaminants of urine, may contain large numbers of typical glitter cells. The question naturally arises whether sterile inflammatory exudate within the nephron may also result in glitter pyuria. Acute glomerulonephritis provides a ready source of urine formed in such tissue, and in 8 children with typical acute glomerulonephritis and negative urine cultures, glitter cells were frequently found, either embedded in hyaline casts or in clumps and occasionally in conglutinated clumps or sheets. Needle biopsy of the kidney in 1 of these patients, a thirteen-year-old boy in the subsiding phase of his disease, revealed a mild polymorphonuclear infiltrate in swollen glomeruli, with no evidence of pyelonephritis. In patients with chronic glomerulonephritis, a disease that lacks a strong polymorphonuclear element in its cellular response, glitter cells have been frequently seen, but in this situation urine cultures are positive and kidney biopsy almost invariably demonstrates a coexistent pyelonephritis.[13] We have found this true of a wide variety of renal diseases — for example, amyloid and Kimmelstiel–Wilson disease. In patients with known pyelonephritis, glitter cells, or at least blue-staining polymorphonuclear leukocytes, are generally

TABLE 2. *Effect of Tonicity on Granular Motility.*

MEASURED SPECIFIC GRAVITY	CONCENTRATION	GRANULAR MOTILITY
	milliosmols/liter	
Glucose:		
1.002	50	+
1.009	100	+
1.015	200	+
1.021	300	+
1.028	400	+ (slightly)
1.040	600	0+
1.054	800	0*
Saline solution:		
1.003	200	+
1.007	381	+
1.011	576	+
1.014	792	0*
1.057	—	0*
Normal urine:		
1.005	300	+
1.010	334	+
1.026	921	0*

*Reversible by dilution with distilled water.

present if several urines are examined. The word of caution must be added that biopsy has repeatedly shown active pyelonephritis when urine sediments were virtually cell free on one or two examinations, thus necessitating repeated examination of the urine.

Finally, the question of separating pyelonephritis from cystitis on the basis of urine sediments remains. Pertinent observations are few, and there is no conclusive evidence to date. Sternheimer and Malbin[4] described a patient with pyelonephritis and cystitis in whom urine from the renal pelvis consisted largely of glitter cells, whereas bladder urine contained a majority of orange-staining polymorphonuclear leukocytes. Reubi et al.[14] observed a patient whose pelvic urine was free of glitter cells whereas bladder urine contained "30 per cent granular motility cells." This observation is somewhat ambiguous since no mention was made of differential nuclear staining in the cells that lacked granular motility. We have observed 2 patients with simultaneous collections of bladder and pelvis urine. In both, 80 per cent of the polymorphonuclear leukocytes from the pelvis had blue nuclei and granular motility, and the same proportion of bladder cells exhibited orange nuclei and immobile granules.

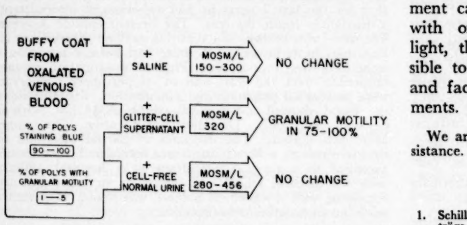

FIGURE 1. *Effect of Various Solutions on Immobile Granules.*

CONCLUSIONS

Glitter cells must at present be considered damaged polymorphonuclear leukocytes that have found their way into urine by a variety of routes and circumstances as described. Although their absence from the sediment on *repeated* examination is evidence against pyelonephritis, their presence should raise the clinician's suspicion of pyelonephritis. The observations presented here suggest caution against overinterpretation of the glitter-cell phenomenon as "specific" for or "pathognomonic" of renal infection. In urines of concentrations greater than 600 milliosmols per liter the presence of polymorphonuclear leukocytes with blue-staining nuclei and immobile granules probably has the same significance as the typical granular-motility cell. Although the brownian movement can easily be seen in unstained preparations with ordinary microscopy and reduced incident light, the Sternheimer–Malbin stain makes it possible to recognize abnormal nuclear-dye absorption and facilitates recognition of all other formed elements.

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MEDICAL PROGRESS

HEALTH IN COLLEGES AND UNIVERSITIES (Concluded)

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Emergency and Elective Surgery

Any college-health administration has other surgical conditions to contend with than those of trauma. To be sure, most of these pertain to superficial and minor surgical infections. In our experience less than 2 per cent of the enrolled students require hospitalization[16] for all causes: medical, surgical and psychiatric. It is of interest, however, that two thirds of the hospital admissions outside the infirmary are for surgical conditions and that among such admissions, in our experience, are appendicitis, acute pancreatitis, intestinal obstruction, renal calculus, perforated gastric and duodenal ulcers and spontaneously ruptured spleen — truly surgical emergencies.

To demonstrate that one cannot anticipate routine surgical diagnoses, and that unusual pathology may be anticipated, 2 cases are briefly cited.

CASE 1. L.E., a healthy 18-year-old member of the freshman wrestling team, returned from an off-campus contest by bus with his teammates. Fortunately, he did not compete, having won his 123-pound-class match by default. He had been suffering all day with an increasingly severe abdominal pain referable to the left upper quadrant, and reported to the infirmary, where he was admitted. The staff surgeon had been called by the resident on duty and had considered the possibility of a subcapsular splenic hemorrhage, referring the patient to one of the hospitals affiliated with the medical school. Before this evening the student had not sought medical advice. A carefully taken history revealed that he had been on a very restricted diet "to make his weight class," where 10 pounds in weight had to be lost in 12 days. At the 9th day a weight check revealed the loss of only 5 pounds, so that he added dehydration and steam-bath therapy. At "weigh-in" on the morning of the meet he weighed exactly 123 pounds. Immediately after this, he devoured 2 breakfasts, totaling 2244 calories, and 1 hour later left-upper-quadrant pain radiating to the back developed. He suffered with this for 10 more hours before seeking medical treatment.

On hospital admission, largely because of the dietary indiscretion, a blood amylase test was made and reported at 52 Russell units (normal, 8 to 18 units). This clarified the diagnosis and ruled out a splenic lesion. "Treatment consisted of gastric suction, atropine, penicillin and streptomycin, parenteral infusions of fluids and electrolytes and sedation with barbiturates."[17] The patient was desperately ill for 3 days, after which he made a gradual recovery, having been transferred on the 10th day to the college infirmary fully convalescent. After 1 week's convalescence, he returned to his dormitory, resuming his full academic routine but deprived of all sports activity.

He was readmitted to the infirmary 2 months later with acute hepatitis, staying for 3 weeks, and since then has remained well.

CASE 2. N.A.W., a 27-year-old former graduate student and assistant track coach, was admitted to the college infirmary with a gradually increasing "gnawing" pain in the area of a healed appendectomy scar. He stated that his appendix had been removed some 20 years previously, but that for the last 2 years he had experienced intermittently a discomfort inside the scar. The present episode, however, was more noteworthy. No vomiting and no diarrhea at any time had been present, but there had been a sensation of some distention on occasion. Physical examination revealed tenderness over the scar, and at its periphery borborygmi were present on palpation and auscultation. Examination of the blood showed a white-cell count of 14,000, with 76 per cent neutrophils. Urinalysis was negative. The temperature was normal. The diagnosis of partial intestinal obstruction due to a fibrous band was considered, and transfer arranged to a surgical consultant at a hospital affiliated with the medical school. At operation an acute ruptured appendix, with a walled-off abscess, was found. The patient made an uneventful convalescence.

The history of prior appendectomy is not infallible.

The health service must be staffed and equipped to handle such cases at all times. It must provide ambulance service by contract or otherwise for emergencies and for occasions on which large crowds foregather (football games, commencement and so forth). It must also have qualified surgeons on call and make available affiliated hospital services that will satisfy the college administration, the students and the parents concerned. Certain colleges are fortunate in possessing university hospitals on the campus, but where no such institution is available, particularly in rural areas, arrangements must be worked out in detail with the nearest best qualified hospital. A college infirmary should no longer be considered an adequate facility for the carrying out of major surgical procedures. This has been the attitude at Harvard for over twenty years.

This institution of 10,000 enrolled students has consistently averaged 250 minor surgical operations a year. The ten most common surgical procedures carried out in the College Infirmary for the past three years have been as follows: excision of sebaceous cyst; drainage of furuncle or superficial abscess; suture of superficial lacerations; excision of nevus; application of plaster of Paris for simple fracture; sigmoidoscopy; Winograd operation for ingrown toenail; excision of superficial tumor (verrucca, fibroma, basal-cell carcinoma); excision of foreign body; and evacuation of clot from external hemorrhoid.

This list represents surgical conditions that might be termed office-practice surgery or might be performed in an outpatient department at a general hospital. Any surgical condition of more serious na-

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ture is referred to 1 of 75 surgical consultants, representing the various surgical specialties.

The necessity of providing in a health plan for surgical care to the student population is shown in our experience for operating a surgical outpatient clinic, separate from that which operates with the athletic teams. Certain hours in each weekday must be provided on regular schedule, the services of a qualified surgeon being available. Our experience has shown that 21 per cent of the outpatient visits require the services of a surgeon, and that 66 per cent of the evening calls at the Infirmary (when the outpatient department is closed) are calls for a visiting staff surgeon. For any college administration to consider that one man highly qualified in the field of medicine can be responsible for "all sorts of conditions of men" of college age and to be qualified to treat such conditions himself would be a grave misconception. Experience has shown that a group of consultants in the various specialties of medicine, surgery and psychiatry is a necessary requirement in a college-health program, and that if the college can finance a good and complete program with student support, representatives of these specialties in medicine should be on the active staff, part or full time on regular schedule.

Mental Health of College Students

Since the last progress report two and a half years ago, new mental-hygiene programs with full-time psychiatrists in charge have been established in several universities, among them those of Nebraska, North Carolina, Pennsylvania, Chicago and Colorado. In some institutions these programs are entirely new; in others they are extensions of previously existing smaller programs. The chief obstacles to more rapid development in other institutions are those of finances and the shortage of psychiatrists with experience or training in this field.

Harrison[18] recently studied 179 students who left Yale University from 1947 to 1952 because of emotional problems. These students were classified into four diagnostic categories — namely, character and behavior disorder (67 cases); psychoneurosis (57 cases); psychosis (52 cases); and transient personality reaction (3 cases). Character and behavior disorders were most frequent among the freshmen whereas psychoses tended to increase in a linear fashion from the freshman year to the graduate-school group. At the time of leaving, more than half the students with character and behavior disorders, 44 per cent of those with psychoneuroses, and only 21 per cent of those with psychoses were in academic difficulties.

By August, 1955, 86 of the 179 (48 per cent) had returned to Yale, and 59 (69 per cent) of them remained to graduate. The students who were in academic difficulty at the time of leaving Yale were the least likely to return.

Harrison concluded that, "Three factors had a significant effect on a student's chances of successfully completing his career upon return to Yale: (a) graduate students did better than any other group, (b) students in academic difficulty were much more likely to leave again, and (c) those students given a diagnosis of character disorder were just as likely to fail again as to succeed, while students who left because of a neurotic or psychotic disturbance had a better than three-to-one chance of succeeding once they returned."

The term character disorder as used in the Yale study refers to students who "act out" their impulses instead of developing neurotic symptoms. "Their life, in contrast to the neurotic, who suffers from typical symptoms, is dramatic; it is not just a private affair of the patient; it involves his environment."[19] The behavior of such persons is poorly motivated, frequently illogical and often self-destructive in its long-term effect, and consists of the substitution of neurotic behavior for unconscious fantasies and neurotic symptoms. The patients learn slowly if at all from experience.

One of the most helpful monographs that has appeared in recent years designed to aid in the understanding of the problems of the years of late adolescence and early maturity is by Erikson.[20] The author uses the term *ego identity* to denote certain comprehensive gains that the individual, at the end of adolescence, must have derived from his preadult experience to be ready for the tasks of adulthood. Identity formation begins where the usefulness of identification ends. The young person must at some point begin to make his own choices and be himself. The individual is recognized by the community, and, in turn, the community feels recognized by him, or it may reject him if his behavior is such that he does not seem to care about it. Crises in identification occur often in late adolescence in many of which the patients can be said to suffer from *acute identity diffusion*. "A state of acute identity diffusion usually becomes manifest at a time when the young individual finds himself exposed to a combination of experiences which demand his simultaneous commitment to *physical intimacy* (not by any means always overtly sexual), to decisive *occupational choice*, to energetic *competition*, and to *psychosocial self-definition*." Erikson comments that these disturbed young people cannot make an adjustment of their own (they cannot "make use of the institutionalized moratorium provided in their society") but go to psychiatrists, priests, judges or recruitment officers to be given an authorized, if ever so uncomfortable, place in which to wait things out. Every college psychiatrist will profit from a careful study of this monograph. He will be reminded of many of the acute problems of his patients.

The Committee on the College Student of the Group for the Advancement of Psychiatry issued in

May, 1955, a very valuable report on personality development in college students.[21] This small monograph discusses not only the psychology of the college student but also the role of the administration and the faculty in his emotional maturation. The role of a counselor is briefly delineated. It contains a bibliography of some of the most useful references in the field. The report was designed to supplement an earlier one on the role of psychiatrists in colleges and universities, issued in 1950.[22]

Mental health in colleges and universities was the subject of eight lectures in the Lowell Institute series given early in 1956.[23] In these lectures the entire field was summarized, with emphasis on the role of mental health in colleges, how it relates to total health, the organization of a program, and its relation to other departments of the institution.

The emotional maturation of the college student, the effect of faculty attitudes on students, how student customs, morale and attitudes are related to intellectual development, how the college student responds to stress, and common background factors in students working ineffectively were all discussed at length. In the discussion of counseling and psychotherapy an attempt was made to define the two processes in terms both of the training and of the intent or purpose of the person engaging in one or the other of these processes.

The writer makes a strong plea for a more adequate and comprehensive effort to develop a greater awareness of emotional factors in the educational process, especially in professional schools that are training people to engage in pursuits that have much to do with interpersonal relations. The professions with the greatest responsibilities as well as opportunities in this regard include law, medicine, teaching, the ministry, business and physical education, though others might well be added to this list — notably, engineering.

Dental Health of Students

As part of a new emphasis on dental-health activities rather than routine dental treatment, all first-year students at Harvard were given bite-wing x-ray studies as part of their entering physical examination. Of 1031 freshmen so examined 754 (73 per cent) were found to have dental defects. Of these, 135 had defects in urgent need of treatment if loss of teeth was to be avoided. This experience is somewhat similar to that of one of us (D.L.F.), who found that in his department at the Massachusetts Institute of Technology over a period of eight years the entering class averaged about 60 per cent with dental defects. Whether these experiences are typical for the college student of all parts of the country, we do not know.

Research

By slow degrees physicians and health educators in the field of college health have begun to develop an awareness of the role that research may play in the furtherance of better understanding of students' health problems. The Committee on Research at the Fourth National Conference on Health in Colleges found that problems most often of interest to physicians working in student health included gastrointestinal disorders, infectious mononucleosis, late adolescent diabetes, problems of personal adjustment, psychiatric disorders, reactions to stress, early evidence of degenerative diseases, upper respiratory infections and public relations. The Committee indicated that research in college-health departments should, in general, be directed to problems that are to some extent peculiar to college students and not to those occurring with equal frequency in the general population.

Further observations of this group included the idea that research and service are mutually supporting and that teaching and research are similarly complementary. More research is in progress in large universities and in those connected with medical schools than in the small colleges. Little support, either moral or financial, is actually available in most institutions.

A committee of the American College Health Association, under the chairmanship of Summerskill, of Cornell University, is actively developing large-scale research projects in which several universities may participate. An example of this is a study of rheumatic fever and rheumatic heart disease being organized in conjunction with the Public Health Service.

Experience in attempting to meet the health needs of the larger universities, particularly those with enrollments of more than 5000, indicates that it may be possible to outline the general type of organization that is desirable for an optimum health program. Such a skeletal design is here presented, with the idea that it may be helpful to college administrators who have the responsibility of setting up or reorganizing their health departments. Appropriate modifications should, of course, be considered in institutions with specialized enrollments or curricula.

Fundamental to the most effective use of a health service is its location. The central clinic and infirmary should preferably be located near the center of daytime activity on the campus. The offices of the professional staff, the laboratories and the infirmary should be in the same building if valuable time is to be conserved, on the part of both the patient and the physician or nurse.

The professional organization should be in charge of a physician, the director of health, who has a regular faculty appointment. To carry on his duties without becoming so involved in clinical problems that his department fails to function smoothly, he needs associates in each of several broad areas. Our personal preference is a separation into services, medical, surgical, psychiatric, dental, environmental-health and safety, and nursing, with a chief for each

one. This chief may be full or part time, depending upon the size of the institution, and the director may assume one of these posts if the college is not too large. When the department is large and complex, a business manager is a necessity and will more than justify his position in terms of financial savings. Economy is effected in increased efficiency and by freeing the time of the physicians so that they can devote their energies primarily to medical pursuits.

The Director of Health

The responsibility of the physician in charge of the health program is to keep himself so well informed of all conditions throughout the institution that have a bearing on the maintenance of health that he may utilize the abilities of his staff effectively in promoting health, preventing illness or injury when possible, and giving adequate treatment to those who become disabled or distressed from any cause. To carry out this threefold program, he should personally participate to some extent in each activity, — health education, prevention and treatment, — but he should have experts on his staff to aid him in specialized procedures. He supervises the programs of tuberculosis control and of immunization against preventable diseases. His clinical duties should not be allowed to take so much time as to prevent him from carrying out his entire health program in an optimum manner. He should establish numerous channels of communication with students, employees, faculty members and officers of administration. He must have the privilege of seeing the top administrative officials of the institution whenever he considers it proper without making anyone think that he is "getting out of channels."

The Chief of Medicine

This physician, who may be the health director in the smaller universities but a separate individual in the larger ones, cares for patients in the infirmary, arranges the clinic schedules, plans preventive medical procedures in consultation with the director and the chief of environmental health and safety, acts as consultant for the director when he is needed, and may act for the director when he is not available for any reason.

The Chief of Surgery

He should be available at regular intervals at the health center for routine consultations regarding surgical or potentially surgical disorders. He should be on call for other members of the staff when they encounter emergencies in his field. He should have general supervision of the medical aspects of the athletic program, including oversight of the work of the trainers. All determinations of fitness for athletic participation by students should be made by him, in consultation with the health director when that is desired or appropriate. He should be selected by the health director subject to the approval of the athletic director.

The Chief of Psychiatry

In addition to a program of treatment for persons in the college or university who are handicapped by emotional conflicts, the college psychiatrist and his assistants should be available for consultation by students, faculty members and administrative officials concerning general problems in which feelings, motivation or apparently illogical behavior are points at issue. Under ordinary circumstances about half the time of the chief of psychiatry should be occupied in seeing patients directly, and the remainder in conference with administrative officials, parents, counselors, student-government leaders or anyone connected with the institution who is involved in a situation with disturbed interpersonal relations. He should act as a consultant to counseling agencies on the campus, serving as a liaison between them and the health service. He should work in close association with the psychologic testing service.

The Chief of Environmental Health and Safety

This staff member, who may or may not be a physician, should have general oversight of sanitary inspection of the dining halls, the dormitories and in some communities the rooming houses patronized by students. He should be familiar with ventilation, lighting, heating or any conditions in the college buildings that have some relation to health. He should be responsible for a safety program in which participation of college personnel should be as wide as possible. He should be aware of the main research projects that are being conducted in various parts of the university, consulting with the directors of these projects when appropriate. This is frequently a matter of considerable delicacy, because an abrupt or tactless approach to the project director may make him think that his freedom of action is being impaired. The hazards associated with the handling of radioactive materials are a particular source of responsibility and interest. He should carry on a continuous program of safety education designed to minimize the possibility of injury, not only those of a physical nature but also those from toxic materials, such as benzene, mercury and carbon tetrachloride.

The Chief of the Dental Service

The dentist in charge of a college dental health program (and his assistants) should examine all entering students, advise appropriate treatment when indicated, maintain a list of suitable consultants to whom students may be referred, supervise the work of the dental hygienists and see that appropriate aid is available when anyone in the college suffers injury

to normal teeth. At Harvard, an institution located in an urban setting, it has been found advisable to limit dental work for the most part to diagnosis, emergency dentistry, prophylaxis and dental education. The expense and other complexities caution against the development of a complete and all-inclusive dental-care program.

The Chief Nurse

No person can be so valuable in maintaining a helpful environment for students to recuperate from illness as the nurse in charge of the college infirmary. Firm, friendly discipline, a sense of humor, warmth and understanding, dignity and high professional standards are all qualities that no nurse can ever possess to perfection but that can be cultivated to the great good of the entire college-health program. The chief nurse not only may administer the professional aspects of the college infirmary but also, because of her somewhat unusual perspective of the college, she can be of great help in improving the health program, through her attendance at staff meetings, counseling activities with students and participation in the life of the college or university community.

The Business Manager

A few years ago the Director of the Health Service at the University of Minnesota said that any health service whose budget exceeded $200,000 should have a business manager, if the director's time was to be wisely used.[24] Experience at the universities of Minnesota and Michigan, as well as at Harvard, have borne out the wisdom of this point of view.

The business manager, or executive assistant, acts as the agent of the director in all matters that are not immediately professional. He prepares the annual budget, attends to payroll matters, selects secretarial and other nonmedical personnel, takes care of much routine correspondence, carries out the necessary investigations on which suitable answers to many letters depend, administers any health-insurance program and listens to students and others who have suggestions or criticism. In hundreds of ways he helps keep the health department running smoothly, with good communication and co-ordination between its members as well as with the people who are being served. The more he can be identified and familiar with the professional program, without actually making decisions in the medical field, the more he will be able to interpret the work of the department in such a way as to win the confidence of the physicians, nurses and students.

A desirable function of a large student-health service, one whose importance is not always fully appreciated, is that of demonstrating to the students how complicated the maintenance of good health and treatment of illness and injury is under modern conditions and how necessary it is to have active co-operation of practically all members of the community if a program is to be successful. The more the students themselves can be kept informed of health planning, the better this function can be served. We have found them to be most helpful when they are asked to act in advisory capacities. As they become community and national leaders later on, it is hoped that exposure to good health practices in the college or university will lead them to expect and strive for nothing less in their own communities.

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MEDICAL INTELLIGENCE

CANDIDA ALBICANS ENDOCARDITIS AFTER AORTIC VALVULOTOMY*

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THE frequency of endocarditis after cardiac surgery is not generally appreciated, and this is considered to be an uncommon complication. Only 9 cases have previously been reported, all of bacterial origin.[1-6] A case in which endocarditis due to *Candida albicans* developed three months after aortic valvulotomy was observed. We believe that this is the first case of postvalvulotomy endocarditis due to this unusual organism and are reporting it to re-emphasize the importance of endocarditis as a sequela of cardiac surgery.

CASE REPORT

A 40-year-old man was admitted to the Philadelphia Veterans Administration Hospital on October 11, 1955, with a history of anginal pain of 6 years' duration, recently increasing in persistence and intensity until it was nearly constant. A diagnosis of rheumatic heart disease with aortic stenosis had been made in 1941, and since that time he had complained of dyspnea, fatigue and, during the preceding year, lightheadedness and dizziness. One syncopal attack occurred in 1954.

Physical examination revealed characteristic findings of aortic stenosis. Roentgenologic examination of the heart showed concentric hypertrophy of the left ventricle and calcification of the aortic valve. An electrocardiogram was consistent with hypertrophy of the left ventricle.

Because of the severity of the symptoms and their failure to improve with medical management, valvulotomy was performed on November 9. The valve was markedly stenotic and calcified, but a satisfactory opening was accomplished by finger fracture through an aortic approach. Postoperatively, the patient received penicillin, 300,000 units twice daily, and streptomycin, 0.5 gm. twice daily, for 15 days, and no antibiotics were given thereafter. There was improvement in both the symptoms and the objective findings, and he was discharged from the hospital on December 14.

He returned on February 3, 1956, with fever, chest pain, pain and tenderness in the right upper quadrant of the abdomen, hepatosplenomegaly and widespread embolic phenomena. Because he was extremely ill, several venous-blood cultures, 1 arterial-blood culture and a bone-marrow culture were taken, and therapy was started with penicillin in a dosage of 4,000,000 units a day. On the 4th hospital day there were findings suggestive of embolism to the left leg and renal infarction; streptomycin was added to the therapeutic regimen. Two days later the original blood cultures were reported to be growing a monilia, subsequently identified as *C. albicans*.

A transient drop in temperature and apparent clinical improvement at this time were thought to represent a response to conventional antibiotic therapy. Because of this and the rarity of the organism as an etiologic agent in endocarditis, the possibility was entertained that the fungus was either a contaminant or a secondary invader. For the next few days all blood cultures were reported negative for monilia, and a false sense of security resulted. It soon became apparent, however, that the infection was not under control. The temperature rose, and monilia was reported to be growing in all the blood cultures previously reported to be negative as well as in a culture of purulent material obtained from a small abscess on the right palm at the site of an Osler node. No satisfactory therapeutic agent for systemic moniliasis was available. Nystatin (Mycostatin), which is reported to be effective against monilia in the intestinal tract, does not provide adequate blood levels for systemic infections. We were advised that an available parenteral preparation of nystatin was too unstable and potentially toxic for use.[7] Before an adequate test of a new antifungal antibiotic, Amphotericin B,§ currently under investigation, could be made, the patient's condition deteriorated rapidly. On the 12th day there were increased embolic phenomena; tonic convulsions with opisthotonos developed, and he became comatose. Only a few doses of the new antibiotic were given by Levin tube. Respiratory paralysis necessitated a tracheotomy and a respirator, and the blood pressure had to be maintained with levarterenol (Levophed). The patient died on February 15.

At autopsy, performed 24 hours after death, a densely calcified, stenotic aortic valve was found, with a fracture valvulotomy extending into the right anterior cusp as far as the aortic ring. There were extensive, well organized, grayish-white vegetations on the aortic valve (Fig. 1). The other valves were not involved. There were widespread mycotic emboli to the vessels of the brain, myocardium, liver, pancreas, kidneys, small and large intestine and the extremities. A thrombosed mycotic aneurysm of the left renal artery was present. The immediate cause of death was extensive subarachnoid and parenchymatous hemorrhage, possibly secondary to the rupture of 1 or more mycotic aneurysms of the cerebral vessels. Post-mortem culture of the vegetations on the aortic valve grew *C. albicans*, and the fungi were visible in direct smears of the material from the valve. Fungi were also demonstrated in histologic sections of the tissues. A blood culture grew only coliform organisms, considered to be post-mortem invaders. A culture of *C. albicans* from the aortic-valve vegetations was lethal to mice.

FIGURE 1. *Gross Appearance of the Heart at Autopsy, Showing Extensive, Well Organized, Grayish-White Vegetations on the Aortic Valve.*

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Discussion

Endocarditis occurs more frequently after cardiac surgery than is generally realized. This complication is not mentioned in a review of the clinical results in 500 cases of mitral valvuloplasty by Ellis and Harken.[8] One large clinic, however, has already seen 22 cases, or approximately 1 per cent of their series,[9] and conversation with other workers suggests a similar rate of occurrence. Dalton and his associates[6] report 3 cases in 150 patients, or 2 per cent. Of the 9 cases of postoperative endocarditis that have been reported, 6 have been due to antibiotic-resistant *Staphylococcus aureus* and 1 to *Pseudomonas aeruginosa*. In 2 cases the blood cultures were negative although the clinical picture was consistent with the diagnosis of bacterial endocarditis.

Monilial endocarditis is rare, only 17 cases having been reported.[10-25] In 5 cases the diagnosis was based only upon the demonstration of fungi in histologic sections of the vegetations; in 3 cases the organism was identified as candida,[15,16] and in 9 cases the diagnosis was established ante mortem by positive blood cultures and confirmed by the demonstration of fungi in the tissues at autopsy.[17-25] The organisms involved were *C. parakrusei, C. albicans, C. guilliermondi* and *C. krusei*. In the present case *C. albicans* grew in ante-mortem and post-mortem cultures and was also demonstrated in histologic sections of the tissues.

The significance of a laboratory report of a rare organism of low pathogenicity is often doubted. The question may be raised whether it is a secondary invader with the primary infectious agent unidentified. Such doubts should not interfere with appropriate therapy. Although in several of the cases of monilial endocarditis in the literature the fungus may have been a secondary invader that followed a bacterial infection[17-19] the infection in the case reported above appears to have been primary. No bacteria were present in the ante-mortem blood cultures, and no antibiotics that might have suppressed bacterial growth and permitted the emergence of an antibiotic-resistant organism had recently been given.

The role of antibiotics in favoring the development of infections with antibiotic-resistant organisms of low pathogenicity has received much attention. The observation of moniliasis in patients treated with antibiotic therapy was made by Harris,[26] Woods and his associates[27] and others. Some workers have found that antibiotics enhance the growth of *C. albicans* in vitro and increase the mortality from mycotic disease in laboratory animals,[28,29] but this was not confirmed by others.[30,31] Kligman[31] believes that clinically significant infection with *C. albicans* after suppression of the antibiotic-susceptible flora is infrequent and usually not too serious. On the other hand severe infections have occurred.[23,32-36] The pathogenicity of organisms of low virulence may rise when their numbers are increased by the suppression of the other flora, and severe and even fatal infections may follow if the host resistance is reduced by other serious disease or unusual circumstances, of which cardiac surgery may be one example. Whether the monilia was present in small numbers originally or arose from an outside source is difficult to establish with certainty. Seven of the 17 cases of monilial endocarditis reported were in drug addicts who administered their drug intravenously. In several others a local monilial infection elsewhere in the body was present, which may have given rise to hematogenous spread. No focus was identified in the case reported above, and cultures of the skin, oropharynx, stool and urine were negative, suggesting that the organism was most probably of exogenous origin.

Summary and Conclusions

A case of unusual interest is presented in which *Candida albicans* endocarditis followed aortic valvulotomy.

Monilial endocarditis is rare, this being the eighteenth case reported in the literature.

Endocarditis follows cardiac surgery in probably 1 or 2 per cent of cases, and its frequency is not generally appreciated, only 9 cases having been reported.

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STUDIES IN CYSTIC FIBROSIS OF THE PANCREAS*

A Simple Test for the Detection of Excessive Chloride on the Skin

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THE measurement of the sodium and chloride concentration in body sweat is now a well established diagnostic procedure in the study of patients suspected of having cystic fibrosis of the pancreas. The original and important observation of the elevated sweat electrolytes in patients with cystic fibrosis by Darling et al.[1] imposed conditions for the collection of sweat that limited the application of their findings to the few institutions where the temperature and humidity of a specially constructed room could be carefully controlled (temperature of 90°F., and humidity of 50 per cent). Shwachman, Dooley and Higgins (1954) devised a practical method of performing "the sweat test" whereby the body and extremities of the patient are enclosed in a plastic suit, the test being conducted in a room without special consideration for the careful control of temperature or humidity. Our experience with this procedure, whose diagnostic value has been indicated elsewhere,[2] will be described in another publication. The "sweat test" performed routinely in our laboratory for the past two years requires thirty to ninety minutes for the collection of the sweat, and an additional ten minutes for the chemical assay of chloride and sodium. Although the initial studies of thermally induced body sweat included the measurements of sodium, potassium and chloride concentration, it became apparent that the measurement of either chloride or sodium would suffice for diagnostic purposes.

This report describes a test for chloride that is carried out by application of the test medium to a surface of the body. The chloride present on the body surface is registered on the surface of the medium. This is an immediate test and in practice amounts to having a finger or hand or foot impression made on an agar surface containing the test ingredients. This test simplifies the diagnosis of cystic fibrosis from a very complicated one to an instantaneous office procedure.

PREPARATION OF TEST MEDIUM

To prepare 500 ml. of the mixture, 25 gm. of agar is dissolved in 500 ml. of boiling water. When the agar is melted 4.2 gm. of silver nitrate is added to the agar and thoroughly stirred. Then 2.5 gm. of potassium chromate is added, and the mixture stirred for a few minutes. The warm, red mixture is poured into plastic Petri dishes or onto a cardboard surface and permitted to harden. The chloride test medium prepared in this way can be stored in the icebox or at room temperature for a number of days without any significant alteration. However, when exposed to warm temperatures, the agar tends to dry out. When the medium is poured into a Petri dish it resembles a blood-agar plate because of the reddish color. These plates or pads may be stored in a sealed plastic bag for prolonged periods without deterioration.

PERFORMANCE OF THE TEST

A finger or hand imprint or, in small infants, a toe or foot impression is made directly on the surface of the agar plate. Very gentle pressure is needed. When little chloride is present on the skin surface, as after the hands are washed in water and dried, the imprint is barely detected on the surface of the plate. If considerable chloride is present on the skin surface, an intense whitish-yellowish discoloration occurs immediately (Fig. 1 and 2). We have rated the reactions +, ++ and +++. A concentration of less than 60 milliequiv. per liter will produce little or no reaction (+) whereas one of over 250 milliequiv. will give an intense discoloration (+++). Once the finger impression is made one cannot use the same finger again until a replacement of sweat occurs, a matter of ten or twenty minutes. In small babies it may be more convenient to test the foot than the hand. Various parts of the body or the surface of various organs may be tested in a similar fashion. One may obtain a rough correlation of the chloride content of the imprint by comparing the imprint made with the finger dipped in a solution of known concentra-

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tion of sodium chloride. Excess liquid on the dipped finger is removed by gentle waving in the air before its application to the plate. In infants less than three or four weeks of age the imprint is barely visible, indicating lack of sweating in the newborn period. One may standardize the test procedure by obtaining the initial finger imprint, followed by washing and drying the hands and retesting after remaining in a warm room for twenty minutes. The results noted in this report are imprints taken during August and September.

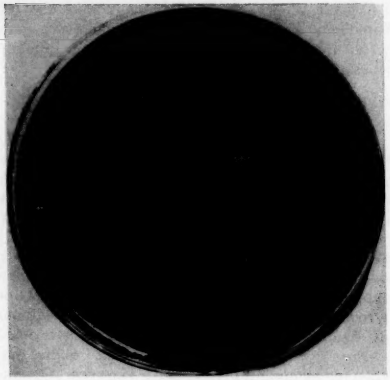

FIGURE 1. *Hand Impression of a Healthy Three-Year-Old Child (Reaction +).*

RESULTS

Table 1 lists the results obtained in a large number of persons tested. Of 140 patients with proved cystic fibrosis of the pancreas, all but 2 gave a +++ reaction. In these 2 the reaction was a ++. In 1 case a ++ reaction was noted in a patient who had a high normal value for sweat sodium and chloride as measured by our standard procedure of performing the sweat test. In the second case the body-sweat electrolyte concentration was abnormally elevated. A +++ reaction was obtained in 4 children who were suspected of having cystic fibrosis on clinical grounds. The sweat test was high normal in 1 case and average normal in the 3 others. Duodenal intubation yielded normal results in 2 patients. These children gave a history of excessive sweating. However, the great majority of the sick infants and children from the various wards of the hospital and outpatient department, as well as a group of healthy children and adults, gave a + reaction (86 per cent); a smaller number (12 per cent) gave a ++ reaction. When the siblings and parents of patients with cystic fibrosis were considered a number showed a +++ reaction, a finding in line with our previous studies, in which approximately 20 per cent of the parents of patients with cystic fibrosis had elevated sweat electrolytes. The results in newborn infants showed a uniformly minimal reaction, and for this reason infants under four weeks of age were excluded from our report. Two infants with meconium ileus were tested during the first week of life. A very faint reaction appeared, indicating again the lack of sweating of infants in the newborn period.

DISCUSSION

From our limited experience with this new procedure the possibility of recognizing patients with cystic fibrosis of the pancreas becomes a simple matter. It also provides an opportunity of screening large numbers of children for cystic fibrosis. This test is simple, inexpensive and painless, takes little time and requires no skill to perform. It is suggested that, in interpreting the imprint, one at first test a few healthy subjects and compare the imprints with that of the patient. The technician may serve as a control. One may also use a standard solution

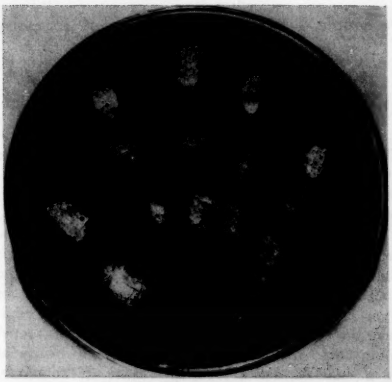

FIGURE 2. *Hand Impression of a Five-Year-Old Child with Cystic Fibrosis of the Pancreas (Reaction +++).*

of 100 or 150 milliequiv. of sodium chloride for comparison. The test may be repeated at frequent intervals if there is a question of interpretation. We have repeated a number of tests on the same subject on various occasions, and the reaction noted is usually the same. Two healthy adults were tested on numerous occasions, with a ++ reaction, and on one occasion each gave a +++ reaction. Although the fingers from the right and left hands generally yield the same result one may encounter conditions in which this similarity does not prevail, as in patients with unilateral muscular, neurogenic or vascular disturbances.

One may enumerate a number of factors that influence the chloride content of sweat.[3] The concentration of chloride in palmar sweat is higher than that in body sweat. In a few measurements we found palmar sweat from healthy subjects to contain the same concentration of electrolytes as noted from the body sweat of patients with cystic fibrosis. Secretion of palmar sweat is influenced by psychic stimuli whereas that of body sweat is not. The influence of environmental temperature is such that increasing the skin temperature may increase the chloride content of sweat. There is also a seasonal difference, with a greater salt content in winter than in summer. If sweating occurs the rate and duration will also influence the salt content. Finally, the diet, the state of renal and adrenal function and the presence of fever, dehydration and possibly malnutrition are additional factors that may influence the salt content of sweat. The few discrepancies noted in patients with normal body-sweat electrolytes and high finger-sweat chloride should be viewed in the light of these remarks, or perhaps such patients should be regarded as having a greater psychic response than that ordinarily encountered.

The absence of perceptible sweating in the neonatal period eliminates the possibility of using this test to detect infants with intestinal obstruction in the first few days of life that is due to meconium ileus. Any procedure that would help establish the diagnosis preoperatively might prove helpful to the surgeon. Elevated sweat electrolytes develop in all babies with meconium ileus.[4] We plan to determine at what age the test becomes positive although we suspect that it does so between three and five weeks of age.

The application of body secretions such as saliva, tears, nasal secretions, bronchial secretions and other biologic materials directly to the plate to obtain a rough estimate of the chloride content appears feasible. It should be noted, however, that the plate will only yield an approximate estimate of the chloride content in regions and in materials insufficient or unsuitable for quantitative analysis.

One may apply the same principle for the presence of iodides, in which case the resultant color is canary yellow.

The large number of + + + reactions in parents and siblings is in accord with the genetic data indicating that these individuals represent the heterozygote, assuming that one gene is involved in the transmission of this disease as a mendelian recessive. In 2 previously unrecognized cases a + + + reaction in siblings led to the diagnosis of the disease.

The occurrence of + + + reactions in 138 of 140 patients with cystic fibrosis tested, and in 4 sick children who did not have cystic fibrosis, indicates that one should view all children with this reaction with care and proceed with other studies guided by the clinical condition of the patient. We feel reasonably safe in discarding the diagnosis of cystic fibrosis in a child who gives a + reaction by this test.

TABLE 1. *Results of Fingerprint Readings on the Chloride Test Plate in 642 Patients.*

REACTION	TEST SUBJECTS					
	140 PATIENTS WITH CYSTIC FIBROSIS	77 HEALTHY INFANTS & CHILDREN	140 HEALTHY ADULTS	103 CHILDREN WITH MISCELLANEOUS DISEASES	39 SIBLINGS OF PATIENTS WITH CYSTIC FIBROSIS	143 PARENTS OF PATIENTS WITH CYSTIC FIBROSIS
+	0	65	128	82	20	78
+ +	2	12	11	17	13	43
+ + +	138	0	1	4	6	22

SUMMARY AND CONCLUSIONS

A new test for detecting the approximate chloride content of the skin surface is described. The test medium is composed of silver nitrate and potassium chromate suspended in an agar base. The majority of healthy and sick children yielded a + reaction, whereas 138 of 140 patients with cystic fibrosis gave a + + + reaction that was due to the increased chloride content on their skin.

It is safe to assume that a patient who yields a + reaction under ideal conditions for the test does not have cystic fibrosis. The application of this rapid, inexpensive and painless procedure for a mass screening program is indicated. In performing the test one should be careful to ascertain the reliability of the test plate by using adequate controls. Environmental and other conditions affecting the patient, which in turn alter the chloride content on the skin, must be considered in the interpretation of the test.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42471

PRESENTATION OF CASE

A seventeen-year-old schoolgirl was admitted to the hospital because of oliguria.

Two and a half weeks previously she noted urinary urgency and frequency with burning on urination. One week later there was a sudden onset of fever with chills, anorexia, nausea, diarrhea, vomiting, pain in the back and diffuse abdominal pain. The urine was smoky; the sediment contained 10 to 15 white cells and 10 to 15 red cells per high-power field. The temperature rose to 105°F.; dyspnea was noted, and she entered another hospital. At that time the urine was smoky, with an albumin of more than 100 mg. per 100 ml.; the sediment contained 10 to 15 white cells and a rare red cell per high-power field; a culture grew out *Escherichia coli (Bacillus proteus)* that was resistant to all antibiotics except Furadantin. Examination of the blood revealed a hemoglobin of 16.5 mg. per 100 ml. and a white-cell count of 28,300, with 94 per cent neutrophils. The urea nitrogen was 23 mg., and the bilirubin 0.35 mg. per 100 ml. The sodium, potassium and chloride were normal. Gantrisin was given for three days. She became oliguric, the urinary volume ranging from 0 to 340 ml. daily. A lumbar puncture yielded clear cerebrospinal fluid that contained 2 red cells per cubic millimeter; the total protein was 29 mg. per 100 ml. Therapy included about 1000 ml. of dextrose daily given intravenously, erythromycin and, later, Furadantin. The blood urea nitrogen gradually rose to 335 mg. per 100 ml. The urinary specific gravity ranged between 1.010 and 1.015; the albumin remained greater than 100 mg. per 100 ml.; the sediments contained rare to 8 or 10 red cells and an occasional to 40 or 50 white cells per high-power field; during the day before admission dyspnea was again noted.

A large number of teeth had been extracted three and a half weeks previously. The patient had had sexual intercourse a month before entry. The last menstrual period had occurred two weeks before admission. She denied any instrumentation of the uterus.

Physical examination revealed a very dyspneic, pale, thin girl who was rational. Examination of the optic fundi was negative. Diffuse medium pulmonary rales and rhonchi were audible. The heart was enlarged to the left. The cardiac sounds were forceful. A gallop rhythm was heard at the apex. The abdomen was full, firm and moderately tender. No organs or masses were palpable. No peristaltic sounds were heard. There was no peripheral edema. The deep tendon reflexes were depressed.

The temperature was 97.4°F., the pulse 120, and the respirations 34. The blood pressure was 160 systolic, 120 diastolic.

The urine was acid and gave a + + test for albumin; the specific gravity was 1.010; the sediment contained 7 red cells, 50 white cells with frequent clumps and numerous bacteria per high-power field; a culture grew out abundant *Pseudomonas aeruginosa (B. pyocyaneus)*. Examination of the blood revealed a hemoglobin of 11 gm. per 100 ml. and a white-cell count of 21,200, with 94 per cent neutrophils. The nonprotein nitrogen was 235 mg. per 100 ml. The sodium was 130 milliequiv., the potassium 10.3 milliequiv., the chloride 97 milliequiv., and the carbon dioxide 16 milliequiv. per liter. A blood culture showed no growth.

The patient died suddenly two hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT L. BERG*: This case lends itself well to backward analysis, the technic enjoyed by many of our engineer and mathematical friends, who, knowing the final answer, are able to make retrograde analyses of the solution by use of a well known factor. It is clear that at the time of the sudden death the patient had a remarkable elevation of potassium, in all likelihood to a level that is frequently associated with fatal arrhythmias or asystoles. I believe the hyperkalemia was the actual cause of death, although the only clinical finding that went along with it was the depressed tendon reflexes. It is, nevertheless, common for patients to deteriorate rapidly under these circumstances without other symptoms of hyperkalemia.

The hyperkalemia, in turn, was probably produced by acute tubular nephrosis, which is suggested by the oliguria associated with a moderate hypertension and resulting in renal failure during the second week. The high potassium, the acidosis, the anemia, the elevation of the white-cell count to 21,200, the albuminuria of moderate degree, the urinary sediment and the specific gravity were all consistent with acute

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tubular necrosis. The only other cause that has to be considered is acute glomerulonephritis. There was less albumin in the urine than one would expect with glomerulonephritis, fewer cells in the sediment and no casts. The specific gravity was low rather than normal or high as it would be in glomerulonephritis. There was no retinopathy or peripheral edema. I think the evidence is strongly in favor of acute tubular necrosis with renal failure.

In spite of the organisms in the urine I shall not seriously consider a diagnosis of pyelonephritis or perinephric abscess in view of the acuteness and severity of the renal failure.

It will be necessary to return later to the organisms in the urine and the absence of peristalsis at the time of admission. Patients with acute tubular nephrosis often have abdominal tenderness, but it is uncommon to have entire absence of peristaltic activity.

Now we approach the real mystery — that is, the nature of the events preceding the acute renal failure. These events consisted of fever and chills, anorexia, nausea, vomiting, back pain and abdominal pain. The major disorders that precede acute tubular necrosis can be put under a half dozen headings, as Strauss and Raisz[1] and Merrill[2] have done in their respective monographs. The first category is trauma, as in battle shock or with thermal injury. The second is hemolysis, or myoglobinuria, resulting in the plugging of the tubules with pigment material. I might point out that if one does not take the precaution of looking at the serum or plasma the hemolysis may be missed; the hemolyzed blood will determine as hemoglobin in the ordinary technic. Therefore, in a blood sample it might appear as a normal hemoglobin, when, in fact, it was lower than normal. The third category is hypotension of any degree continued over a period of time. The others are hemorrhage, severe infection and exposure to chemical toxins.

In the protocol there are only one or two clues to the cause of the tubular necrosis. A large number of teeth were extracted several weeks before admission. This raises the question of a subacute bacterial endocarditis and conditions associated with it, but it would be unusual for subacute bacterial endocarditis to represent the degree of infection that is followed by acute tubular necrosis. I am inclined to discard it on that basis. Tubular necrosis can be associated with acute bacterial endocarditis, but it seems unlikely to me that the patient could have had an acute bacterial endocarditis and not have had more signs and symptoms of it.

There was no evidence of any of the other major categories. Although an unexpected event could have occurred, it seems unlikely. I am inclined to think, therefore, that there was a concealed cause — concealed not by the pathologist but presumably by the patient. Suicide and attempts at abortion are the two chief processes that patients might conceal. There was nothing to suggest suicide although many agents that are used to produce abortions have also been used as suicidal agents. I shall not consider suicide further. In fact, the only clue is that the patient had had sexual intercourse a month before admission. Moreover, there is the statement that she denied instrumentation. The very fact that the statement is included is important, since it may be intended as a clue. When a young woman has acute tubular necrosis without an apparent antecedent cause, certainly one should always inquire about abortion.

The technics that she might have used in attempting to abort herself include agents administered by the oral and by the local route. I have looked into the books of poisoning and legal medicine about abortifacients and have found this a liberal education. There are a number of different drugs and preparations for use by mouth that have had a long and presumably extensive career. The ones that have a historic significance are certain plant products, of which there are an enormous number. I was fascinated to discover that the preparations known as Russian and Spanish flies (they are, indeed, small flies) were approved both as aphrodisiacs and as abortifacients in the ancient literature. That has poetic significance. In addition, the oils of aloe, colocynth, turpentine, pennyroyal, nutmeg, hellebore, tansy, rue, savin, cedar, thyme, cotton-root bark, laburnum and numerous others have all been used as abortifacients. Apparently, almost any drug that is sufficiently irritating to the gastrointestinal musculature, — and many of these are cathartics fundamentally, — when taken in excess, may be hoped so to excite the uterus that it will discharge its contents. Among the emetics are the halogenated derivatives, carbon tetrachloride and chloroform, which are also used as abortifacients, but they often do not produce their kidney effects for four to ten days. I think that if the so-called menstrual bleeding that this patient had represented the result of an abortive attempt, the latent period probably was too long for these agents.

In addition to these cathartics, there are the oxytocics — ergot, Pituitrin and oxytocin. A third group of drugs used as abortifacients include the benzene derivatives, which work in a way that we do not clearly understand. In common with quinine, they produce not only increased muscular contractions but also hemolysis, with the formation of methemoglobin. Finally, there are certain oxidizing agents that may be used either locally or by mouth and produce their effects apparently by their strong oxidizing properties. These include potassium permanganate and the chlorates.

In this patient I think the postulate of an oral abortifacient is not necessary because there is good evidence that she had some problems that could only have arisen from local applications — namely, the abdominal pain and distention, as well as the high fever and other evidence of local infection. I think,

therefore, that I can turn my attention to the local abortifacients. I should imagine that in an attempt to inject some locally sclerosing or scarring solution into the uterus she, as most seventeen-year-old girls would have done, missed the mark and perforated the uterus or the cul-de-sac in the vaginal vault and thus produced a peritonitis. I believe a drug must have been used in addition to something like a slippery-elm stick because it is unlikely that a seventeen-year-old girl who had induced a peritonitis by instrumentation would have such acute tubular necrosis on this basis alone. I suspect that there was an added insult to account for that.

What local effects might have been produced? It is well known that attempts at manipulating and instrumentating an early pregnancy by inexpert people are associated in a very high proportion of cases with perforation of the uterus, which is soft and easily perforated at this point and results not only in septic endometritis, peritonitis and commonly endocarditis if streptococci or staphylococci are introduced but also, sometimes, in a purulent thrombophlebitis. She may have had not only a peritonitis associated with the instrumentation but also remote effects as a result of spread of infection. Furthermore, there can be a purulent thrombophlebitis, with septic infarcts in the lungs and later elsewhere. There may be a hemolytic reaction if *Clostridium perfringens (B. welchii)* is involved. Occasionally, there may be just a bland thrombus at the site of injury, with peripheral pulmonary emboli. If soapy water is used under pressure, air from the bubbles may be forced into vessels, to produce death by air embolus.

I think that local peritonitis can account for what happened, if, in addition, I am allowed to assume that it was produced by an attempt to inject a sclerosing material. This is obviously highly speculative, but it seems to me probable that in the attempt to instrument the uterus, organisms were introduced into the urinary tract, either by direct extension or because the peritonitis produced inflammation about the urinary tract. I think that is the explanation for the organisms in the urine, and I think that the peritonitis will readily explain the severe pain in the abdomen and back.

Among the agents used locally, in addition to the potassium permanganate and chlorates, there are the phenol derivatives, such as lysol and creosol. Many of the heavy metals have been used — commonly, arsenic trioxide, zinc chloride, lead, ferric chloride and mercuric chloride. Other local escharotics include phosphorus, oxalic acid, the alkalis and formaldehyde. It is of some interest that in the paper of Swan and Merrill[3] on acute tubular necrosis, of 85 cases, 2 or 3 were induced by a hemolytic abortifacient. Jetter and Hunter[4] have pointed out that potassium permanganate used as a local scarring agent to induce abortion can be followed by the accumulation of blood pigments in the renal tubules. This, then, brings up the question of whether or not a hemolytic abortifacient was used. I think that there is not enough evidence for it. If there had been a hemolytic abortifacient, the anemia should have been more profound. The degree of anemia was entirely consistent with acute tubular nephrosis alone. I believe that at autopsy there were evidences of perforation, either of the uterus or of the vaginal vault, some evidence of scarring or necrosis within the uterus, which may have been discolored by permanganate — but I cannot implicate permanganate as a hemolytic agent because there was no evidence of hemolysis — and the characteristic evidence of acute tubular necrosis.

DR. BENJAMIN CASTLEMAN: Dr. Berg, when do you think the process began, before or after the urinary frequency?

DR. BERG: I should imagine afterward.

DR. CASTLEMAN: You do not explain the urinary urgency.

DR. BERG: I think that was honeymoon cystitis *sine* honeymoon.

DR. H. WALTER JONES, JR.: Dr. Berg, I wonder whether the Gantrisin could be implicated in any way and whether this could have been an acute papillary necrosis.

DR. BERG: As far as the Gantrisin is concerned, I was informed that further questioning revealed that the drug had not been given until she was in the other hospital. Whether or not she had had Gantrisin as treatment for what I take to have been cystitis is difficult to establish.

DR. JOHN B. STANBURY: I think that that point needs to be clarified. I talked to the family physician, who told me that after the chill, but several days before the patient went into the hospital, he gave her Gantrisin, but only a few tablets.

DR. BERG: It is certainly true that even with small amounts of sulfonamides there may be enough precipitation of crystals in the urine to induce the same situation. However, I should think it most unlikely that it could explain the degree of fever before entry to the other hospital — and so I tended to believe that there was another process in addition.

DR. JAMES C. DAVIS*: By tubular necrosis, what particular tubules do you have in mind?

DR. BERG: As I understand it, although at first and for some time this was thought to be lower-nephron involvement, it has now been demonstrated that there is a spotty involvement of all portions of the tubular system, with necrosis and rupture of the basement membrane in various portions, so that no single portion of the tubules is involved.

DR. DAVIS: I should like to comment on that in a moment.

DR. ALFRED KRANES: I wonder, in view of what has just been said about an induced abortion,

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whether Dr. Berg may have meant acute cortical necrosis.

DR. BERG: No; I mean acute tubular necrosis, or what used to be called lower-nephron nephrosis.

DR. CASTLEMAN: Dr. Kranes, do you think that it was acute cortical necrosis?

DR. KRANES: I think that is a possibility since the question of abortion has been raised. Acute cortical necrosis is not an uncommon sequel to abortion.

DR. BERG: The picture is more consistent with lower-nephron nephrosis, if you want to use that term.

DR. KRANES: I do not think that there is a characteristic clinical picture that would differentiate the two; certainly, the urinary findings will not.

CLINICAL DIAGNOSES

Uremia.
Pulmonary edema.
Overwhelming sepsis.
? Sepsis in pelvis.

DR. ROBERT L. BERG'S DIAGNOSES

Abortion, with peritonitis and endometritis.
Acute tubular necrosis.

ANATOMICAL DIAGNOSES

Lower-nephron nephrosis.
Pyelonephritis.

PATHOLOGICAL DISCUSSION

DR. DAVIS: In this case the patient was not pregnant; the uterus was completely normal, and the history of the menstrual period was presumably genuine. The interesting pathologic process was in the kidneys, which did, in fact, show the picture of pigment nephrosis, or lower-nephron nephrosis, as Dr. Berg suggested, but, in addition, they showed a healing acute pyelonephritis. Scattered through the cortex and occasionally in the medulla were some yellow-white areas that histologically showed infiltration by chronic inflammatory cells. Presumably, the antibiotic that had been given, the Furadantin, had cured the acute nephritis, which probably was responsible for the pain in the back, for which she was admitted to the hospital. In addition, there were the changes of what personally I should like to call lower-nephron nephrosis. In the distal tubules in the cortex there were quite conspicuous brown casts, which were granular and completely filled the lumen of the tubules (Fig. 1). These casts were quite different from the occasional hyaline casts that can be observed with simple ischemia of the kidneys. In the medulla in the connecting tubules exactly similar casts, which were characteristic of pigment nephrosis or hemoglobinuric nephrosis, were found. The proximal convoluted tubules were dilated but were otherwise normal. The proximal tubules did not show any necrosis in ordinary histologic sections. The glomeruli gave no evidence of acute glomerulonephritis, which had been considered. We do not know definitely what the source of the hemoglobin that was being excreted was. There was nothing to suggest that abortifacients were given because the patient was not pregnant; it is conceivable that she may have thought that she was and had given herself abortifacients. Perhaps it would be kinder to assume that the lower-nephron nephrosis was caused by the Gantrisin, which is known to cause hemolysis and may end in lower-nephron nephrosis or pigment nephrosis. In fact, there were some crystals in the kidneys compatible with sulfonamide crystals in the distal convoluted tubules; the crystals were doubly refractile, with Maltese crosses in the center, a picture identical with sulfonamide crystals, though an identical appearance caused by leucine is occasionally seen after incompatible blood transfusions.

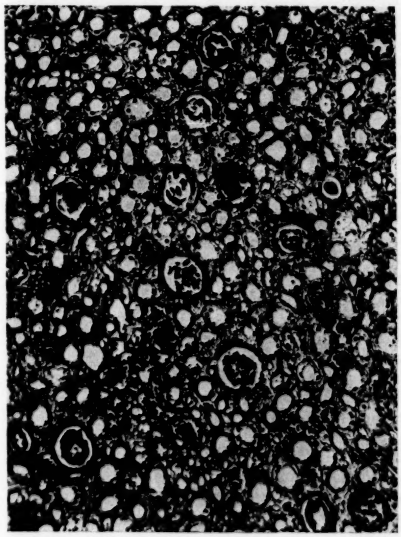

FIGURE 1.

I should like to plead that the term acute tubular necrosis is not satisfactory. To begin with, it is redundant, for necrosis is always acute; it is never chronic — calling it acute is like talking about purulent pus or sanguineous blood. I do not think the clinician, on the basis of the history of the urinary findings in this case, could tell what kind of lesion the kidney showed. The case clinically could equally well have been cortical necrosis. Therefore, the clinical diagnosis, I think, should be acute renal shut-

down. That describes the fact that the patient has anuria. Pathologically there seem to be two different conditions: one is necrosis of the proximal convoluted tubules, which can be reproduced by pure ischemia and appears to be of the same nature as renal cortical necrosis but of a lesser degree; the other is the type described here, with pigment casts containing hemoglobin or rarely myoglobin in the lower nephrons. There is actually no necrosis, or at least not conspicuous necrosis, in the tubules at the time that the patient becomes anuric. If the patient lives for ten to fourteen days, as many of them do before dying of anuria, there will be necrosis of all the tubules that contained the casts, the necrosis having the appearance of being produced mechanically by the pressure of the casts in the lumens. That is hardly a reason for calling the process tubular necrosis, since the cast apparently causes it. The lesions in the proximal part of the tubules are apparently simply secondary to the plugging of the nephron lower down. The tubules in these cases are conspicuously dilated. The lesion can be produced by acute hydronephrosis just by tying off the ureter, and the tubular necrosis that Oliver and his associates[5] have described in the proximal tubules does not appear until several days or even a week or so after the onset of the condition and apparently is purely secondary. Acute tubular necrosis, therefore, appears not to be a satisfactory term, for the necrosis is hardly the primary cause of the condition; it is merely a phenomenon secondary to the appearance of casts in the lower nephron. Apparently, the excretion of hemoglobin in a kidney slightly damaged by some other process results in these casts. The normal kidney can excrete hemoglobin; but the kidney damaged by any cause, such as a transitory ischemia insufficient by itself to result in severe kidney damage, or lowering of blood pressure by surgical shock, or possibly, as in this case, an acute pyelonephritis, cannot excrete hemoglobin, which precipitates and forms casts in the tubules. Personally, I think that the term lower-nephron nephrosis, which is now in considerable disrepute, is a good one, for the lesions are most conspicuous in the lower nephrons. Furthermore, I think this process is fundamentally different from lesions of the kidney seen in uncomplicated shock, which are those of cortical necrosis.

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CASE 42472

Presentation of Case

First admission. A seventy-five-year-old retired carpenter entered the hospital because of progressive weakness of the right arm and impairment of speech.

According to the family he had been well until about two months previously, when he began to complain of "numbness" and stiffness of the right hand and arm. After a week he was no longer able to use the right hand for fine movements, such as writing or shaving. At about this time, it was observed that he no longer seemed interested in going out or in "puttering about" in the house. On one occasion, about five weeks before admission, he suddenly called out to his wife for help because he felt "dizzy"; she observed that he "did not seem to know where he was," although he apparently could speak clearly, and there was no facial asymmetry or additional weakness of the limbs. Some four weeks before admission, he seemed unusually lethargic and no longer as careful of his personal appearance as he had previously been. Two weeks before admission he gave up reading the newspaper (his wife thought from "loss of interest") and began to remain increasingly longer in bed. Speech at this time was reported to be clear and intelligible. In the following week, he became confused over the use of a knife and fork. Two days before admission his speech became difficult to understand ("garbled"), with some misuse of words, and the right foot dragged as he walked. On the day of admission he complained of severe generalized headache.

His general health had previously been good. He had had injuries to his limbs at work, without residual disability. There had been an episode of pleurisy and effusion twenty-seven years before entry. Six years before the present admission, he was admitted to the hospital for bilateral saphenous-vein interruption because of varicose veins. He gave a history of some exertional dyspnea for "several years," but no chest pain. On examination he was found to have an emphysematous chest with limited expansion and a Grade 1 systolic murmur heard best to the left of the sternal border in the fourth interspace, but no signs of congestive heart failure or other noteworthy physical findings. The blood pressure was 118 systolic, 88 diastolic. He obtained successful relief by surgery and, after discharge, he had remained generally well until shortly before the present admission. The family history was noncontributory.

Physical examination showed an unkempt man with a vacant facial expression; he denied any symptoms. He was unable to name several common objects, to comply with simple verbal requests or to perform the most elementary arithmetical calculations. Speech, however, was well articulated. He was grossly disoriented in time, could not remember

the names of most of his children and gave the name of the President of the United States as "McKinley." When asked to demonstrate the use of familiar objects, such as a comb, a pencil, a flashlight and a key, he was unable to do so. He could see, although he was unable to read large letters, and had evidence of a homonymous hemianopia on the right. The optic disks and retinal vessels were not remarkable. The pupils were equal at 3 mm. and reacted well to light. Ocular movements were full to testing, but he did not at any time look to his right spontaneously. There was a spastic right-sided hemiparesis, most severe in the right arm (with very weak wrist and finger movements), with mild weakness of the right side of the face and minimal weakness of the right leg. No abnormality of muscle power, tone or co-ordination was found on the left. There was bilateral reflex grasping. Deep reflexes were moderately active and brisker in the right limbs than in the left. The right plantar reflex was extensor, and the left flexor. No extensive sensory testing was possible, but it was thought that pinprick was less well felt on the right side of the body than on the left, and when both sides were pinched simultaneously, the stimulus on the right was ignored. The neck was supple, and carotid pulsations in the neck were equal.

The findings on general physical examination were much the same as on the admission six years previously. The temperature was 100°F., the pulse 80 and regular except for occasional premature beats, and the respirations 16. The blood pressure was 130 systolic, 80 diastolic.

Examination of the blood revealed a hemoglobin of 16 gm. per 100 ml. and a white-cell count of 17,000. The urine gave a + test for albumin. A lumbar puncture yielded clear, colorless cerebrospinal fluid under an initial pressure equivalent to 100 mm. of water; the fluid contained 10 lymphocytes and 1 large mononuclear cell per cubic millimeter, 60 mg. per 100 ml. of protein and 87 mg. per 100 ml. of sugar and gave a normal colloidal-gold reaction. The Hinton tests on the blood and cerebrospinal fluid were negative. Roentgenograms of the chest gave evidence of pulmonary emphysema, but no other abnormalities in the lungs. The heart was not enlarged. Plain films of the skull showed no osseous abnormalities. The pineal body, visible only in the lateral views, was thought to be displaced slightly forward. An electroencephalogram revealed a focus of delta activity in the left posterior temporal region.

The patient's condition showed no change during the hospital stay. Additional laboratory investigations disclosed normal blood nonprotein nitrogen, calcium, phosphorus, alkaline and acid phosphatase and cholesterol. A cytologic examination of cerebrospinal fluid showed no neoplastic cells. A localization study, using radioactive arsenic, demonstrated no abnormal concentration of activity in the brain.

A pneumoencephalogram, using 40 ml. of air, was performed on the fourth hospital day. This showed some enlargement of the lateral ventricles and an air-filled cavity, 3 by 4 cm., in the left occipital region in communication with the occipital horn of the left lateral ventricle (Fig. 1 and 2). The patient was discharged on the eighth hospital day.

FIGURE 1. *Pneumoencephalogram.*
An irregular air-filled cavity (arrows), continuous with the occipital horn, is demonstrated in the left occipital lobe.

Final admission (three weeks later). After discharge he seemed fairly alert and was able to sit up in a chair, although incontinent and unable to speak. Two nights before admission he began to moan frequently, breathing became increasingly labored, and, although the temperature was not measured, the skin of the arms seemed unusually warm to touch. There was a rapid deterioration of his general condition.

On examination he was awake but unresponsive to voice and appeared seriously ill. He was dehydrated, with cyanosis of the nail beds and harsh breath sounds, with dry rales at the left base. The distal half of the right lower leg was cold, mottled and deeply cyanotic, with absent popliteal and more distal pulsations. Thrombosed superficial veins were found over both forearms. The other general physical findings were as before. Neurologically, there was a flaccid right-sided hemiplegia with increased deep reflexes on the right; reflex grasping and sucking could be elicited.

The temperature was 103.6°F. by rectum, and the pulse 100, and the respirations were of Cheyne–Stokes type at 48 per minute. The blood pressure was 90 systolic, 70 diastolic.

Roentgenograms of the chest showed diffuse mottled shadows in both lungs, consistent with

bronchopneumonia. An electrocardiogram was normal except for occasional ectopic beats.

The patient was given fluids and antibiotics, and anticoagulant treatment was begun. He aspirated

FIGURE 2. *Pneumoencephalogram.*
An irregular air-filled cavity (arrows), continuous with the occipital horn, is demonstrated in the left occipital lobe.

gastric contents on at least two occasions, lapsed into deep coma, and, during a tracheotomy to relieve partial laryngeal obstruction on the fourth hospital day, he died.

DIFFERENTIAL DIAGNOSIS

DR. HERBERT R. KARP*: In essence the problem here is one of establishing the etiologic basis for a severe, widespread neurologic deficit, which evolved over a period of about two months. The symptoms began with numbness and stiffness of the right hand and forearm, which apparently were progressive, so that within a week there was interference with fine movements. To this were added progressive lethargy, disinterest, neglect of personal appearance and then confusion in the use of some common objects, such as a knife and fork, garbled speech and misuse of words. Finally, there was weakness of the right foot and, on the day of admission, a severe generalized headache. From the history, then, we can conclude that this process, whatever it may have been, had extensively involved the left cerebral hemisphere, expressing itself as a right-sided hemiparesis, together with some difficulty in speech, as well as some profound alterations of behavior and mental function.

On physical examination the patient was unkempt and disoriented, with a blank facial expression. He was able neither to name nor to demonstrate the use of common objects, nor to carry out simple verbal commands or to solve simple arithmetical problems. Vision was interfered with, in that he had a homonymous hemianopia on the right. Extraocular movements were full to testing except that he did not look to the right spontaneously. There was weakness of the right arm, greatest peripherally, and a weakness of a milder degree involving the right side of the face and the right leg. Limited evaluation of sensation was interpreted as demonstrating diminished perception of pinprick over the right side of the body, as well as the fact that on bilateral simultaneous stimulation he ignored the stimulus on the right.

At this point, therefore, several further conclusions can be drawn about the anatomical distribution of the cerebral disease. There was probable involvement of the frontal areas as expressed by the alterations in mentation. These behavioral alterations are extremely difficult to evaluate at times, particularly when there is coexisting aphasia and apraxia, which tend to compound the degree of dysfunction. The grasp reflex provides additional evidence of frontal-lobe involvement. The hemiparesis and the homonymous hemianopia point to involvement of the temporoparietal area. The aphasia, the apraxia and the nature of the sensory loss indicate that the cortex was also involved.

In establishing the etiology of the neurologic dysfunction one must consider two possibilities — namely, whether it was neoplastic or vascular. The relentless, relatively rapid progression that characterized the course is very much in favor of neoplasia. I am sure that this was the conclusion reached by the attending physicians, who quite properly embarked on a plan of investigation designed to rule out a space-occupying process that might be amenable to surgical approach. The electroencephalogram, which we can rarely ask to provide us with an etiologic diagnosis, showed a focus in the left posterior temporal region that was certainly compatible with such a lesion. The lumbar puncture, on the other hand, is against this possibility in view of the normal pressure and borderline protein. Here, again, this tool is not infallible, and it is worthy of emphasis that the protein content in particular is helpful only when it is elevated — a normal level carries little weight as evidence against the existence of a tumor.

This might be a logical point at which to ask Dr. Hanelin to review the x-ray films for us.

DR. JOSEPH HANELIN: The pneumoencephalogram shows slight, although definite displacement of the ventricular system toward the right. The lateral ventricles are all moderately dilated. There is an irregular air-filled cavity, approximately 4 cm. in maximal dimension, lying within the left occipital lobe in continuity with the occipital horn on this side (Fig. 1 and 2). It is highly unlikely that the cavity is produced by broken-down tumor in the absence of any marked displacement or distortion of the ventricular system.

DR. KARP: The x-ray film of the chest, which

*Research fellow in neurology, Massachusetts General Hospital.

should always be examined carefully for a source of metastasis when one suspects an intracranial neoplasm, was negative from that standpoint. Similarly, when one considers the extent of the lesion underlying this patient's findings, the skull films and pneumoencephalogram are against tumor. I should have expected much more distortion of the ventricular system, with more evidence of a shift from left to right. Could the cavity in the occipital area represent the remnants of a cyst, thus "decompressing" itself? Cystic degeneration of a tumor is usually ascribed to the tumor's outgrowing its vascular supply and is usually associated with marked edema and swelling, frequently out of proportion to the size of the tumor itself. There was no evidence of this possibility here. However, the absence of shift or distortion of the ventricles, as well as the normal cerebrospinal-fluid pressure, can be misleading in two situations: in early life, when there is widening of the sutures in response to increased volume of the intracranial contents; and in the aged, in whom a pre-existing loss of cerebral mass provides a space into which the brain can expand. So, even though a diffuse intracranial neoplasm is an intriguing possibility, I do not think that it represents the correct diagnosis.

Was this vascular? The history, though perhaps more characteristic of a tumor, is certainly compatible with vascular disease, particularly when the primary source of difficulty resides in a major cerebral vessel, such as the carotid or the basilar artery. Most frequently one sees fleeting symptoms, which seem to herald the appearance of the permanent neurologic deficit. Often, however, the onset is steplike and is seen over a period of weeks or months until the entire clinical picture evolves. The lumbar-puncture findings—namely, the slight response of mononuclear cells and the slight elevation of protein — are certainly compatible with vascular occlusion, as are the findings in the electroencephalogram. The next problem is to determine which vessel or vessels were involved. The bulk of the signs and symptoms could be explained on the basis of a lesion in the distribution of the left middle cerebral artery. To return to the pneumoencephalogram, one would have to postulate that the abnormal collection of air represented the center of an infarcted area that communicated with the ventricle and resulted in the formation of a porencephalic cyst. It is well to mention at this point that cerebral infarction with resultant edema is sometimes accompanied by secondary vascular occlusion, for the cerebral vessels are narrowed by being compressed against the relatively immobile structures, such as the tentorium or the falx. This might explain the diffuseness of the clinical picture. The slight shift in the ventricular system here brings this possibility to mind.

If this was cerebrovascular disease, was it thrombotic or embolic? The history is against an embolic process, though there was at least one sudden episode characterized by the patient's suddenly feeling dizzy and appearing confused. Assuming that the murmur that was heard six years before admission was still present, the coexistence of a murmur and fever in a patient such as this should bring to mind bacterial endocarditis; blood cultures frequently prove quite rewarding under such circumstances. I think it highly unlikely that if he was having multiple cerebral emboli they would all have found their way to the same general area, none traveling to the opposite cerebral hemisphere or to the brain stem. Was it thrombotic? On the basis of the patient's age one could predict that there would be significant atherosclerosis of the cerebral vasculature, but before making this diagnosis, one would like to see some manifestation of vascular disease elsewhere. This was lacking until the last admission, when, in addition to an intensification of the neurologic deficit, there was evidence of occlusion of the arterial tree in the right leg.

In summary, then, I believe that the primary diagnosis is atherosclerosis of the cerebral vessels, with predominant involvement of the left hemisphere in the distribution of the middle cerebral artery. The diffuseness of the lesion, as well as its progressive mode of development, speaks for the left internal carotid artery as the primary site of involvement. The terminal events I should ascribe to general inanition with bronchopneumonia with or without multiple infarction.

Clinical Diagnosis

Thrombosis of left middle cerebral artery.

Dr. Herbert R. Karp's Diagnoses

Cerebral atherosclerosis, with thrombosis of left internal carotid artery.

Cerebral infarction, in distribution of left middle cerebral artery.

Anatomical Diagnoses

Cerebral atherosclerosis, severe, with thrombosis, old and recent, of left internal carotid artery; thrombosis, recent, of left anterior, middle and posterior cerebral arteries; and cerebral infarction, extensive, of left cerebral hemisphere.

Left temporal pressure cone, with secondary hemorrhages, midbrain and upper pons, and pressure necrosis, right cerebral peduncle.

Pathological Discussion

Dr. Leonard Atkins: The pertinent autopsy findings in this case were in the brain, which Dr. Richardson will describe.

Dr. Edward P. Richardson, Jr.: Dr. Karp has given us an excellent discussion of the clinical phenomena occurring in this case, and the diagnosis he arrived at turned out to be the correct one.

The large arteries of the circle of Willis, particular-

ly the internal carotid arteries, showed severe atherosclerosis. There was thrombotic occlusion of the entire length of the left internal carotid artery from the carotid bifurcation in the neck, all the way through the carotid siphon to the circle of Willis; the left common carotid artery was patent. On microscopical examination the most proximal portion of the left internal carotid artery, immediately above the common-carotid bifurcation, was totally obstructed by thrombus of relatively recent appearance. A considerable proportion of this thrombus was made up of platelets and fibrin strands with enmeshed red and white cells and gave no evidence of organization from the wall of the vessel. One portion of it, however, — perhaps a third of the total cross-section of the thrombus, — showed well advanced organization by fibroblasts and newly formed capillaries; this overlay a segment of the vessel wall that was especially severely involved with atheroma, and the organizing connective tissue within the thrombus blended into, and was a part of, similar connective tissue in the vascular intima. The appearance suggested that a recent thrombus had formed upon an older, organizing one and had totally occluded the lumen, whereas the earlier thrombus had merely encroached on the lumen but not obliterated it. The remainder of the left internal carotid artery contained old, organized, well recanalized thrombus, its appearance suggesting a duration of at least many weeks, and possibly of many months or even years. This finding suggests that the patient had had a thrombosis of the upper part of the left internal carotid artery for a long period before the more recent occlusion in the lower portion.

Thrombi of very recent appearance were found in the left anterior, middle and posterior cerebral arteries. These looked as if they had occurred terminally. There was infarction, with ischemic softening, of the entire left cerebral hemisphere. In the frontal, rolandic, temporal and occipital regions, in the distribution of the middle and posterior cerebral arteries, the softening was far advanced, and the brain tissue was so friable that it fell to pieces on removal of the brain from the skull. The medial aspect of the left frontal lobe and a narrow strip of brain tissue bordering the interhemispheric fissure in the distribution of the left anterior cerebral artery was softened, but maintained its form and contours, suggesting that the infarction in this region was very recent and had occurred considerably later than the massive infarction in the remainder of the left cerebral hemisphere. There was pronounced swelling of the infarcted left hemisphere, with a severe degree of herniation of the medial portion of the left temporal lobe through the tentorial opening (left temporal pressure cone) and resulting compression of the midbrain, with multiple small recent mid-line hemorrhages in the tegmentum of the upper brain stem, such as are frequently found with severe temporal herniation.

The vascular system in the right side of the brain was patent, and no lesions were found on the right, with the exception of recent necrosis of the right cerebral peduncle, which can be ascribed to its being crowded against the free edge of the tentorium by the left-temporal-lobe herniation.

In attempting to relate the pathological findings to the clinical events, one is impressed with the steadily progressive course of the illness and the fact that the left internal carotid artery showed occlusions of varying ages, indicating that thrombotic episodes were taking place successively over a considerable period. It may well be that the old occlusion in the upper part of that artery was tolerated for a long while without any symptoms, and that these appeared only after the blood flow in the left carotid arterial system had been further reduced by additional thrombus formation just above the carotid bifurcation. This more recent thrombus may well have increased gradually in size. I think there can be no question that when the patient was first admitted to the hospital with confusion, aphasia and right-sided weakness, there must already have been a considerable degree of infarction of the left cerebral hemisphere. The roentgenographic demonstration of a sizable cavity communicating with the left lateral ventricle is best interpreted as the result of infarct necrosis and cavitation of brain tissue, thereby giving rise to a tissue defect into which air entered during pneumoencephalography — just as Dr. Karp suggested. This interpretation could not be adequately checked on post-mortem examination of the brain because the corresponding region of the brain was so softened and friable that no individual structures, including the ventricular lumen itself, could be identified. The homonymous hemianopia on the right, which was discovered on the initial neurologic examination, may have been due to involvement of the optic radiations in the left temporal lobe, and thus would have been the direct result of the carotid thrombosis, but it is also possible that some degree of left-temporal-lobe herniation existed at that time, which, by compression of the left posterior cerebral artery and resulting infarction of the visual areas in the occipital lobe, could likewise have given rise to the hemianopia. The appearance of the infarction in the left occipital lobe suggested that it was approximately of the same duration as that in the distribution of the left middle cerebral artery; this is evidence in favor of the presence of some left-temporal-lobe herniation at the time of that admission.

Terminally, there were additional thromboses of cerebral arteries on the left, which resulted in infarction of the entire remaining portion of the left cerebral hemisphere. The clinical effect was further worsening of the patient's neurologic state. A significant factor in his death must have been a severer degree of temporal herniation than had previously existed, giving rise to terminal brain-stem hemorrhages.

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SALMONELLOSIS IN GREAT BRITAIN

THE role of the salmonella organisms in human food poisoning, as has been indicated previously in these columns, has become an increasingly important one. The problems thus presented have been analyzed, so far as they pertain to Great Britain, in a timely article by Savage in a recent issue of the *British Medical Journal*.* Figures from the *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service*, to which Savage refers, cite 3 factors in this particular: first, a steady increase in the recorded cases of food poisoning; second, an overwhelming proportion of cases shown to be caused by one or another of the more than 300 serotypes of salmonella, of which *Salmonella typhimurium* is largely predominant, and third, a high proportion of sporadic cases.

As with all types of disease since they have been subjected to modern methods of diagnosis, better recognition of salmonella infections is admittedly partly responsible for the increase and here, also, 3 factors have been responsible. These are: compulsory notification of food poisoning, improved laboratory facilities for the scientific investigation of outbreaks, and an increased interest of public-health officers in the problem, resulting (at least in part) from improved laboratory facilities for the study of these outbreaks. The investigation of the numerous sporadic cases has been both important and frustrating; in the majority no cause has been found although in others a relation to carriers and to infected duck eggs has been elicited.

The majority of the traced outbreaks of salmonella food poisoning come from animal sources, with poultry providing a natural reservoir; duck eggs in particular may be infected from blood stream or oviduct by an organism that is in addition capable of penetrating the shell of the egg during its passage through the common cloaca. Strains of salmonella have also been found in chickens, pigeons, geese, pheasants and turkeys. Pigs and to a less degree cattle are susceptible to infection with salmonella, as are rats, mice, dogs and cats, all of which, when infected, become sources of contamination through the excreta.

From the foregoing facts regarding domesticated birds and their products the importance of eggs, particularly those shipped in bulk, can be adduced. Thus, many thousand samplings of egg powder from the United States revealed salmonella strains in practically 10 per cent, including new hemispheric strains not hitherto found in Britain. Frozen egg mixtures of Chinese origin, however, gave 27 per cent positive results. There is apparently a special risk in dealing with nations behind the bamboo curtain, whose shippers appear to be 17 per cent less virtuous or less health conscious than are those of the United States.

In general the vehicles by which salmonellae have

*Savage, W. Problems of Salmonella food-poisoning. *Brit. M. J.* **2**: 317-323, 1956.

been conveyed to their human host have been meats, — more often "somewhat manipulated" or heavily processed than fresh, — canned foods, milk and milk products, eggs, especially duck eggs, shellfish and sweetmeats. Human carriers cannot be discounted since they may exist in an acute phase during an attack of the disease, as temporary or chronic carriers for a more or less prolonged period after an attack, and as symptomless persons who may not be aware of ever having had an attack.

There is no question that the increase in bacterial food poisoning is real and that it is largely due to various factors of which food prepared in bulk is of great importance, whether consumed in a public eating place or purchased for home consumption. The changes in eating habits that have thus been brought about, whether at home or abroad, require special forms of protection beyond the ordinary inspections of any former period. They require also a more nearly universal education in matters of simple cleanliness and the reasons for it.

THEIR MOTHERS' DAUGHTERS

Some years ago Philip Wylie wrote an interesting book entitled "Generation of Vipers." It caused quite a stir because Mr. Wylie put his finger on several sensitive spots in the national life. One of these was the concept of "Mom," who was accredited with begetting numerous small "momsters," A war was on, and "momsters" often seemed to be the kind of soldiers who broke down in battle. National interest in this subject was aroused, and the best word, if not the final word, was spoken by Dr. Edward A. Strecker, who wrote a marvelous medical and psychologic essay, *Their Mothers' Sons*, in which he reviewed the whole subject from its beginning to its end (and the end was usually some form of neurosis or frustration). It was not a reassuring book, but it cleared the way for a new concept of the part a mother can play in forming or deforming her son's manhood.

A new volume,* written in collaboration with Vincent T. Lathbury, M.D., takes up the same problem and carries it on to its logical conclusion, only this time the searchlights of inquiry are turned on the problems of women and the ways in which mothers can influence daughters for good or ill.

It begins with an extremely interesting list of 90 questions that cover just about all the problems that can arise between a mother and a daughter. The authors do not assume a cynical attitude as the late George Bernard Shaw did in his famous statement, "if there is anybody the well brought up young lady detests more than her older sister, it is her mother," but adopt a lively and realistic view. Their approach is practical, and they use the language of everyday speech rather than the jargon of psychiatry. However, they discuss and come up with good answers to the eternal question, "Who and what are women?" They investigate the relation of mother and daughter, pointing out how the process of severing the umbilical cord can go on for a good many years; they outline various obstacles to successful motherhood in modern life and take into consideration the substitutes for mother and the special problem of the mother who never grew up herself. They have a good deal to say about sex that is sensible and provocative, and they include the fathers of the daughters in the final summing up, which, incidentally, contains a short chapter on the problem of Lesbianism. All in all, they have much to say, and they say it very well.

This book will be instructive to some parents and informative to others. The obstetrician and the gynecologist will find it particularly useful. Psychiatrists are already familiar with some of the ideas that the authors introduce, but as always they will find that Dr. Strecker, a master of his profession, has some new angles and facets to present to the reader. At the very end of the book there are some answers to the 90 questions that thoughtful readers will find quite provocative.

*Strecker, E. A., and Lathbury, V. T. *Their Mothers' Daughters.* 256 pp. Philadelphia: Lippincott, 1956.

REHABILITATION INSTITUTE

At a birthday celebration held at its old homestead, 25 Bennet Street, on October 2, 1956, the Boston Dispensary observed its hundred and sixtieth anniversary, and as evidence that age need not be synonymous with senility chose the occasion to break ground for a new rehabilitation institute adjacent to its older buildings.

The Boston Dispensary, New England's oldest medical institution of its kind, was organized on September 29, 1796, by some 70 philanthropic citizens "for the relief of the sick poor." For a subscription of $5 annually each subscriber was entitled to have 2 patients at a time under the care of the Dispensary. At this time there was no public hospital other than the Pest House in Boston so that needy patients had perforce to be treated in their homes. This necessity had the virtue, according to the subscribers, of being cheaper than hospital care even if such had been available. The Dispensary was incorporated as a charitable institution in 1801. The first staff consisted of one physician, Dr. John Fleet, a graduate of the first class of Harvard Medical School, and one apothecary, Thomas Bartlett, whose shop also served as the Dispensary office. In 1802 the Dispensary service was divided into three districts, with a physician and apothecary for each.

Following the suggestion in 1837 of Oliver Wendell Holmes, then a Dispensary physician, that a central clinic be established to treat more patients at less expense than by sending doctors into their homes, the Dispensary purchased an estate at the corner of Bennet and Ash Streets. Here outpatient service be-

gan in 1856 in a small brick house surrounded by lawns, with the bay at its back door. Service was for those "whose illnesses permitted them to leave their dwellings."

The roster of Boston physicians who have served on the Dispensary Staff over the century and a half includes many distinguished names: James Jackson, John Dixwell, Jacob Bigelow, John Ware, Gamaliel Bradford, Thomas Rotch, William Chenery, Abner Post, Calvin G. Page, Maynard Ladd, Arthur L. Chute, Joseph H. Pratt and William A. Hinton.

The Boston Dispensary pioneered in many fields: home medical service; the employment of visiting nurses in 1814; the first lung clinic, established by Edward O. Otis in 1899; the first food or nutrition clinic in 1918, and the first volunteer service in Boston by members of the "Old Sewing Circle League," the ancestor of the Junior League, whose members assisted in the Dispensary clinics. And now, as evidence of its continued vigor, the Dispensary has embarked on the first rehabilitation institute in New England providing living-in facilities and all the disciplines involved in transforming a handicapped patient into a useful member of society.

PHYSICIANS' FRIEND

Doctors are classically considered as being more kindly disposed to their fellow men than are the usual, run-of-the-mill human beings, intent on their own purposes. It is consequently refreshing to meet occasionally a layman, medically speaking, who has spent his life being unusually kind to doctors.

Mr. George H. Crosbie, who died recently at the age of seventy-three, began selling physicians' liability insurance to the doctors of Massachusetts in 1910, the year of his graduation from Harvard College. He had worked his way through the institution on the Charles by selling insurance, after a year spent as a mail carrier in New Mexico, driving a team of ponies 360 miles a week.

In May of this year, on the occasion of the annual meeting of the Massachusetts Medical Society, Mr. Crosbie celebrated the thirty-fifth anniversary of a closer liaison with the Society, which had in 1921 given his firm a special sort of blessing in relation to malpractice insurance. In other unofficial capacities Mr. Crosbie was friend and advisor to a host of physicians as well as acting in an intermediary capacity in respect to their annual encounters with the Department of Internal Revenue, relative to the dispensing of "opium, coca leaves, marihuana, etc."

•

Uses of Glycerine. — *This article is likely to take its place among the most highly valued, both in medicine and the arts, and the sooner, since a process has been discovered by which it can be rendered pure by distillation. Its remarkable power as a solvent, united to its entire blandness, and freedom from all irritating and fermenting properties, recommend it for a vast variety of uses.*

Boston M. & S. J. *November 27, 1856*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

Williams — Frederick Russell Williams, M.D., of Worcester, died on August 10. He was in his seventy-fifth year.

Dr. Williams received his degree from Long Island College of Medicine in 1905. He was a member of the American Medical Association and a staff member of the Memorial Hospital, Worcester.

He is survived by his widow, two daughters, a sister and six grandchildren.

Watkins — Royal Phillips Watkins, M.D., of Worcester, died on October 19. He was in his ninetieth year.

Dr. Watkins received his degree from Columbia University College of Physicians and Surgeons in 1892. He was past president of the Worcester District Medical Society, a fellow of the American Medical Association and the American College of Surgeons and a member of the New England Surgical Society.

He is survived by three daughters and two grandchildren.

Davis — Bessie D. Davis, M.D., of Cambridge, died on October 18. She was in her ninety-fifth year.

Dr. Davis received her degree from Tufts College Medical School in 1895.

She was a former visiting school physician and was a senior fellow of the Massachusetts Medical Society.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1956

RÉSUMÉ

Disease	Oct. 1956	Oct. 1955	Seven-Year Median
Brucellosis	1	0	1
Chancroid	1	0	1
Chicken pox	369	275	275
Diphtheria	0	2	5
Dog bite	1224	1023	982
Dysentery, bacillary	2	31	15
Encephalitis, infectious	7	2	2
German measles	87	38	54
Gonorrhea	191	176	227
Granuloma inguinale	0	0	0
Hepatitis, infectious	21	34	34
Lymphogranuloma venereum	0	1	0
Malaria	0	0	1
Measles	69	27	107
Meningitis, meningococcal	4	5	5
Meningitis, Pfeiffer bacillus	3	2	2
Meningitis, pneumococcal	2	0	1
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	1	1	0
Meningitis, undetermined	13	9	7
Mumps	457	89	275

Poliomyelitis	9	484	124
Salmonellosis	44	22	20
Scarlet fever	148	110	117
Syphilis	254	182	182
Trichinosis	2	3	3
Tuberculosis, pulmonary	161	119	148
Tuberculosis, other forms	9	11	9
Typhoid fever	2	0	1
Whooping cough	60	77	213

Comment

Diseases below the seven-year median were diphtheria, bacillary dysentery, infectious hepatitis, measles, poliomyelitis and whooping cough.

For only the second time in the State's history, no cases of diphtheria were reported during the month of October.

During October, whooping cough was at the lowest level for this month in the history of the State.

During the month of October, bacillary dysentery was at the lowest level for this month since 1935; poliomyelitis was at the lowest level since 1942, and infectious hepatitis was at the lowest level since 1951.

Diseases above the seven-year median were chicken pox, German measles, infectious encephalitis, mumps, salmonellosis and scarlet fever.

During the month of October, salmonellosis was at the highest level for this month in the history of the State.

During October, German measles and scarlet fever were at their highest level for this month since 1950.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Brucellosis: Fall River, 1.

Dysentery, amebic: Boston, 1.

Dysentery, bacillary: Framingham, 1; Worcester, 1; total, 2.

Encephalitis, infectious: Bourne, 1; Holyoke, 1; New Bedford, 1; North Andover, 1; Norton, 1; Pittsfield, 1; Weymouth, 1; total, 7.

Hepatitis, infectious: Bedford, 1; Boston, 4; Cambridge, 1; Fall River, 1; Fitchburg, 1; Ludlow, 1; Lynn, 1; Northampton, 1; Pittsfield, 1; Springfield, 2; Tewksbury, 1; Waltham, 2; Wellesley, 1; Weymouth, 1; Worcester, 1; Wrentham, 1; total, 21.

Meningitis, meningococcal: Boston, 1; Chicopee, 1; New Bedford, 1; Worcester, 1; total, 4.

Meningitis, Pfeiffer bacillus: Beverly, 1; Lawrence, 1; Lowell, 1; total, 3.

Meningitis, pneumococcal: Leicester, 1; Newton, 1; total, 2.

Meningitis, streptococcal: Southbridge, 1.

Meningitis, undetermined: Amesbury, 1; Beverly, 2; Boston, 1; Cambridge, 1; Chelsea Naval Hospital, 1; Everett, 1; Fall River, 1; Natick, 1; Needham, 1; Springfield, 1; Worcester, 2; total, 13.

Poliomyelitis: Abington, 1; Bourne, 1; Cambridge, 1; Dennis, 1; Medford, 1; Newton, 1; Sherborn, 1; Wareham, 1; Worcester, 1; total, 9.

Salmonellosis: Agawam, 1; Arlington, 3; Attleboro, 1; Belmont, 1; Boston, 3; Braintree, 1; Dartmouth, 1; Fitchburg, 1; Gardner, 2; Hanover, 1; Lexington, 1; Malden, 1; Medford, 1; New Bedford, 2; Newton, 2; Norwood, 7; Salem, 2; Shrewsbury, 1; South Hadley, 1; Spencer, 1; Springfield, 1; Sterling, 1; Waltham, 3; Weston, 1; Worcester, 3; Yarmouth, 1; total, 44.

Trichinosis: Boston, 1; Lynn, 1; total, 2.

Typhoid fever: Dartmouth, 1; Northampton, 1; total, 2.

CORRESPONDENCE

WAFER'S "CLAIM TO FAME"

To the Editor: The editorial, "Freebooting Surgeons," in the September 27 issue of the *Journal* omitted Lionel Wafer's "claim to fame." To quote Mr. L. E. Elliott Joyce (Wafer, L. *New Voyage and Description of the Isthmus of America.* Edited by L. E. Elliott Joyce. Hakluyt Society Works, Series 2, No. 73. 221 pp. London: Oxford, 1934), "The claim of Lionel Wafer to fame rests upon his record of a brief episode of some four months spent among the 'wild Indians' of Darien; and so just is the claim that two hundred and thirty years after the NEW VOYAGE AND DESCRIPTION OF THE ISTHMUS OF AMERICA was printed (1699), his book remains the most authoritative source of information concerning the native folk of south-east Panama."

After Lionel Wafer marched across the Isthmus of Panama to the Pacific Ocean, or South Sea, he cruised around with Bartholomew Sharp, William Dampier and other buccaneers. Soon, this company of buccaneers divided. Wafer joined Dampier's party and recrossed the Isthmus in 1681. Wafer, in his book, states that "on the 5th day of our journey" his leg was injured by a gunpowder accident and that he was forced to remain behind among the Darien Indians with four other straggling buccaneers.

According to John Masefield (Dampier, W. *Dampier's Voyages.* Edited by J. Masefield. 2 vol. London: Richards, 1906), Wafer "lived some months" among the Indians, "who in a manner ador'd" him by reason of his skill in "Physick and Phlebotomy." Wafer lived, he says, "in great splendour and repute" and was painted "in yellow, red, and blue, very bright and lovely" as a mark of the high esteem in which he was held by the Indians.

Eventually, the five men reached the Atlantic side of the Isthmus and rejoined the buccaneers.

Stephen D. Berardinelli
Lieutenant Colonel, MC
United States Army Dispensary
Fort Hamilton
Brooklyn, New York

ENDOMETRIOSIS AND PREGNANCY

To the Editor: As I read over a recent clinicopathological conference I came across two statements that disturbed me slightly. I refer to Case 42372, which appeared in the September 13 issue of the *Journal.*

The case is that of a young woman with known endometriosis in whom a ruptured ectopic pregnancy developed. During the discussion Dr. Coe ventured the opinion that curettage "should have returned decidua." This is an idea that would occur to most physicians as quite logical; however, empirical observations do not bear out its validity. Romney, Hertig and Reid *(Surgery, Gynecology and Obstetrics* **91**:605-611, 1950) found decidua in only 19.1 per cent of 115 endometria associated with ectopic gestation. Possibly, the experience at the Massachusetts General Hospital has been different, but I doubt if decidual transformation of the endometrium is present in more than a third of the cases of ectopic pregnancy by the time the lesion produces symptoms and surgical treatment is carried out.

Also disturbing was Dr. Green's observation that "the known pelvic endometriosis was barely discernible . . . presumably having undergone the typical regression with this pregnancy." I do not question the observation that the endometriosis regressed, but I do not think the implication that such regression is typical of pregnancy is well founded. Although clinical symptoms of endometriosis abate during gestation, the anatomic lesion usually persists; the stromal component often undergoes decidual change (in a normal pregnancy), and the glandular component is often hypersecretory at first and then shows secretory exhaustion. My impression is that ectopic endometrium mimics imperfectly the normal endometrium during pregnancy. However, this impression is based on less than 20 cases.

This note should not be regarded as being hypercritical. Actually, some of my most effective teaching here is based on the Cabot Cases. If I did not value them so highly, I should not have written.

William B. Ober, M.D.
Hackensack, New Jersey

BOOK REVIEWS

The Neurosurgical Alleviation of Parkinsonism. By Irving S. Cooper, M.D., Ph.D. 4°, cloth, 104 pp., with 68 illustrations. Springfield, Illinois: Charles C Thomas, 1956. $8.50.

Charles C Thomas has completed the first edition of an extremely useful guide in carrying out the neurosurgical alleviation of Parkinsonism. It should be of immense value not only to medical students, interns and residents but also to the general practitioners who come in contact with patients with the disease. Needless to say, it is also very important to neurosurgeons. The book demonstrates the fairly simple but thoroughly practical manner of investigating such patients. It also describes the various surgical approaches that have been used in the past.

A clear, to-the-point description of the globus pallidus and its role in Parkinsonism is given.

Dr. Cooper divides the contents of his book in a logical sequence. His discussion of the neurosurgical problems is particularly clear and concise. The diagrams and illustrations are simple but descriptive.

Dr. Cooper should be complimented not only for adding information but also for presenting definitive procedures that at present seem to be valuable links in the chain of treatment. Regardless of whether or not the good results that he reports will be lasting, there is at least a ray of hope for patients with this particularly disabling condition. It is the opinion of the reviewer that Dr. Cooper has made a noteworthy contribution, and the procedure that he has outlined — namely, chemopallidectomy — will continue to provide a wide scope of usefulness in the surgical treatment of such patients.

The publisher, Charles C Thomas, has again demonstrated his ability to produce a monograph of excellent quality.

JAMES L. POPPEN, M.D.

Epilepsy and the Law: A proposal for legal reform in the light of medical progress. By Roscoe L. Barrow; and Howard D. Fabing, M.D. 8°, cloth, 177 pp. New York: Paul B. Hoeber, Incorporated, 1956. $5.50.

Modern medicine marches on, but sometimes its feet become stuck in the mire of legal restraints. Such is the plight of epilepsy and the epileptic patient. Many laws, state and federal, embody the understanding of epilepsy that was common among doctors many decades ago. As stated by Pearce Bailey in his foreword, "This book is part of the literature of indignation." However, study of the contents makes clear the fact that the indignation is well founded. The basis of the book is a detailed documentation of state laws that affect the epileptic patient. For the most part these laws were enacted at a time when epilepsy was believed to be a disease with progressive mental impairment and without hope of substantial medical control. In addition, both the epilepsy and the mental defect were believed to be directly inheritable. The authors have painstakingly analyzed the laws of the 48 states with special reference to marriage licenses, sterilization, driver's licenses and workmen's compensation.

There is the greatest diversity in the content of restraints imposed, none of which define epilepsy. The first eugenic marriage law was enacted sixty-one years ago in Connecticut. Seventeen other states followed suit, some imposing penalties on persons who assist in the marriage. Laws that involve the right to drive a motor vehicle are even more chaotic. In 7 states the physician is required to report cases of epilepsy to health authorities. But report is not required of the alcoholic patient, a much greater offender. Three states require that attacks shall be under control without the use of continued medication. (This seems to be the equivalent of saying the person with a visual defect must not wear glasses.) In the area of employment and workmen's compensation the person with epilepsy shares the problems of those with some physical handicap. However, overemphasis on the degree of danger involved, combined with the stigma attached to the disease, works a peculiar hardship for the epileptic patient. Although 43 states have established second-injury funds, provisions make them generally inapplicable to the epileptic, whose disability is only latent. Claims that arise from such disability should be paid from a fund devoted to encouragement of employment of the handicapped. Federal immigration statutes exclude the feeble-minded insane, those with epilepsy and alcoholism, lepers, prostitutes and paupers. Epileptic persons cannot enter even temporarily for medical consultation, without gaining permission of the Attorney General and posting a bond against becoming a public charge. In addition to the compendium of information not otherwise easily obtainable, the book proposes changes in the wording of laws that would do away with present unfair discriminations. In some cases this involves only omission of the word epilepsy. Because present laws are based on medical opinion as expressed a generation or two ago, physicians of today have a certain responsibility in helping to remove restrictions whose mere existence is a continuing stigma.

This three-year study was initiated by the physicians' American League Against Epilepsy and financed by a grant from the Institute of Neurological Diseases and Blindness. The book is well written and printed and is thoroughly indexed. It constitutes a landmark in the social therapy of epilepsy.

WILLIAM G. LENNOX, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Sleep. By Marie Carmichael Stopes, D.Sc., Ph.D. 8°, cloth, 154 pp. New York: Philosophical Library, 1956. $3.00.

Proceedings of the Annual Meeting: Council for high blood pressure research, American Heart Association: Cleveland, Ohio, November 18-19, 1955. Vol. 4. 8°, cloth, 186 pp., with illustrations, tables and charts. New York: American Heart Association, 1956. $4.50.

Fundamentals of Physics and Applications. By Howard O. Stearns. Second edition. 8°, cloth, 384 pp., with illustrations and tables. New York: The Macmillan Company, 1956. $6.50.

Dynamic Psychiatry in Simple Terms. By Robert R. Mezer, M.D., senior staff psychiatrist, Community Clinic, Massachusetts Mental Health Center and Harvard Medical School. With a foreword by Harry C. Solomon, M.D., medical director, Massachusetts Mental Health Center, and professor of psychiatry, Harvard Medical School. 12°, paper, 174 pp., with 8 illustrations and 3 tables. New York: Springer Publishing Company, Incorporated, 1956. $2.50.

Interesting Cases and Pathological Considerations: And a numismatic suggestion. By F. Parkes Weber, M.D., F.R.C.P., F.S.A. 8°, cloth, 77 pp., with 5 illustrations. London: H. K. Lewis and Company, Limited, 1956. 18s.6d. $2.60.

Pelvimetry. By Herbert Thoms, M.D. 8°, cloth, 120 pp., with 45 illustrations and 3 tables. New York: Paul B. Hoeber, Incorporated, 1956. $5.00.

Organized Home Medical Care in New York City: A study of nineteen programs. By the Hospital Council of Greater New York. 8°, cloth, 538 pp., with 137 tables and 2 maps. Cambridge: Harvard University Press, 1956. $8.00. (Published for the Commonwealth Fund.)

Diseases of the Breast. By C. D. Haagensen, M.D., professor of clinical surgery, Columbia University College of Physicians and Surgeons, and director of surgery, Francis Delafield Hospital, Columbia-Presbyterian Medical Center, New York City. 8°, cloth, 751 pp., with 404 illustrations, 161 tables and 25 charts. Philadelphia: W. B. Saunders Company, 1956. $16.00.

Diseases of the Heart. By Charles K. Friedberg, M.D., attending physician, Mount Sinai Hospital, New York City, and associate clinical professor of medicine, Columbia University College of Physicians and Surgeons. Second edition. 4°, cloth, 1161 pp., with 157 illustrations. Philadelphia: W. B. Saunders Company, 1956. $18.00.

Pediatrics. Edited by Donald Paterson, M.D.; and John Ferguson McCreary, M.D., professor of pediatrics and head, Department of Pediatrics, University of British Columbia. With 36 contributing authors. 4°, cloth, 654 pp., with 192 illustrations, 33 tables and 5 colored plates. Philadelphia: J. B. Lippincott Company, 1956. $14.00.

Modern Medicine Annual 1957: An annual publication containing the articles that appeared in the twenty-four issues of Modern Medicine during 1956. Part One. January 1 through June 15. 8°, cloth, 1047 pp., with illustrations, tables and charts. Minneapolis: Modern Medicine, 1956. (Free.)

Clinical Chemistry: Principles and procedures. By Joseph S. Annino, clinical chemist, Massachusetts Memorial Hospitals, Boston. 8°, cloth, 280 pp., with 15 illustrations and 11 tables. Boston: Little, Brown and Company, 1956. $7.50.

Dermatology. By Donald M. Pillsbury, M.D., professor of dermatology and director, Department of Dermatology, University of Pennsylvania School of Medicine, and director, Commission on Cutaneous Diseases, Armed Forces Epidemiological Board; Walter B. Shelley, M.D., Ph.D., associate professor of dermatology, University of Pennsylvania School of Medicine, chief, Dermatology Clinic, Hospital of the University of Pennsylvania, and area consultant in dermatology, Veterans Administration; and Albert M. Kligman, M.D., Ph.D., associate professor of dermatology, University of Pennsylvania School of Medicine, and associate professor of dermatology, University of Pennsylvania Graduate School of Medicine. 8°, cloth, 1331 pp., with 564 illustrations and 3 tables. Philadelphia: W. B. Saunders Company, 1956. $20.00.

Rosenau Preventive Medicine and Public Health. By Kenneth F. Maxcy, M.D., Dr. P.H. With 27 contributing authors. Eighth edition. 8°, cloth, 1465 pp., with illustrations and tables. New York: Appleton-Century-Crofts, Incorporated, 1956. $15.00.

Military Heritage of America. By R. Ernest Dupuy, colonel, United States Army, retired; and Trevor N. Dupuy, colonel, United States Army. 8°, cloth, 794 pp., with 133 illustrations. New York: McGraw-Hill Book Company, Incorporated, 1956. $10.00. (*McGraw-Hill Series in History.*)

Internal Medicine: A physiologic and clinical approach to disease. By Robert P. McCombs, M.D., professor of graduate medicine, Tufts University School of Medicine, and senior physician, Pratt Diagnostic Clinic-New England Center Hospital. 8°, cloth, 706 pp., with 49 illustrations and 23 tables. Chicago: The Year Book Publishers, Incorporated, 1956. $10.00.

The Human Body: Its anatomy and physiology. By C. H. Best, C.B.E., M.D., D.Sc. (Lond.), F.R.S., F.R.C.P. (Canada), professor of physiology and head, Department of Physiology, and director of the Banting-Best Department of Medical Research, University of Toronto; and N. B. Taylor, V.D., M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C.P. (Canada), M.R.C.S. (Eng.), L.R.C.P. (Lond.), professor of the history of medicine and medical literature, University of Western Ontario, London, Canada. Third edition. 8°, cloth, 723 pp., with illustrations and tables. New York: Henry Holt and Company, 1956. $6.75.

Roentgen Signs in Clinical Diagnosis. By Isadore Meschan, M.D., professor of radiology and director, Department of Radiology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem College, North Carolina. With the assistance of R. M. F. Farrer-Meschan, M.B., B.S. (Melbourne, Australia). 4°, cloth, 1058 pp., with 2216 illustrations and 28 tables. Philadelphia: W. B. Saunders Company, 1956. $20.00.

A Manual of the Common Contagious Diseases. By Philip Moen Stimson, M.D., professor of clinical pediatrics, Cornell University Medical College, and consulting pediatrician, New York and Roosevelt hospitals and Hospital for Special Surgery, New York City, Meadowbrook Hospital, Hempstead, Bergen County Hospital, Bergen Pines, Norwegian Lutheran Hospital, Brooklyn, Norton Memorial Hospital, Middletown, and St. Francis Hospital, Poughkeepsie; and Horace Louis Hodes, M.D., pediatrician-in-chief and director, Department of Pediatrics, Mount Sinai Hospital, New York City, clinical professor of pediatrics, Columbia University College of Physicians and Surgeons, and consulting pediatrician, North Shore Hospital. Fifth edition, thoroughly revised. 12°, cloth, 624 pp., with 83 illustrations, 10 plates and 16 tables. Philadelphia: Lea and Febiger, 1956. $8.50.

Athletic Injuries: Prevention, diagnosis and treatment. By Augustus Thorndike, M.D., chief surgeon to the Department of Hygiene and Department of Athletics, Harvard University, and lecturer on surgery, Harvard Medical School. Fourth edition, thoroughly revised. 8°, cloth, 252 pp., with 113 illustrations and 31 tables. Philadelphia: Lea and Febiger, 1956. $4.50.

Dictionary of Poisons. By Ibert Mellan and Eleanor Mellan. 8°, cloth, 150 pp. New York: Philosophical Library, 1956. $4.75.

They Remember America: The story of the repatriated Greek-Americans. By Theodore Saloutos. 8°, cloth, 153 pp., with 5 tables. Los Angeles: University of California Press, 1956. $3.50.

Human Generation: Conclusions of Burdach, Döllinger and von Baer. By Arthur William Meyer. 8°, cloth, 143 pp., with 9 plates. Stanford: Stanford University Press, 1956. $3.50.

Williams Obstetrics. By Nicholson J. Eastman, professor of obstetrics, Johns Hopkins University School of Medicine, and obstetrician-in-chief, Johns Hopkins Hospital. Eleventh edition. 8°, cloth, 1212 pp., with illustrations and tables. New York: Appleton–Century–Crofts, Incorporated, 1956. $14.00.

New Bases of Electrocardiography. By Demetrio Sodi-Pollares, M.D., chief, Department of Electrocardiography, National Institute of Cardiology of Mexico, and professor of cardiovascular clinics, National University of Mexico, Mexico City. With the collaboration of Royall M. Calder, M.D., editor, English translation, clinical professor of medicine, Baylor University College of Medicine, consultant, Brooke Army Medical Center, electrocardiologist, Baptist Memorial Hospital, and physician and cardiologist, San Antonio, Texas. 8°, cloth, 727 pp., with 523 illustrations and 3 tables. St. Louis: The C. V. Mosby Company, 1956. $18.50. (Translated from the recent revision of the third Spanish-language edition.)

The Psycho-Medical Guide to a Lifetime of Good Health: The promise of psychosomatic medicine. By Curt S. Wachtel, M.D. 8°, cloth, 318 pp. New York: Psycho-Medical Library, Incorporated, 1956. $5.00.

Medical Effects of the Atomic Bomb in Japan. Edited by Ashley W. Oughterson, clinical professor of surgery, Yale University School of Medicine, and attending surgeon, Grace–New Haven Community Hospital; and Shields Warren, M.D., pathologist, New England Deaconess Hospital, and professor of pathology, Harvard Medical School. 8°, cloth, 477 pp., with illustrations, tables and charts. New York: McGraw–Hill Book Company, Incorporated, 1956. $8.00. *(National Nuclear Energy Series,* Manhattan Project Technical Section, Division VIII — Volume 8.)

Chronic Illness in the United States: Care of the long-term patient. Vol. 2. By the Commission on Chronic Illness, June, 1949, to June, 1956. 8°, cloth, 606 pp., with tables. Cambridge: Harvard University Press, 1956. $8.50. (Published for the Commonwealth Fund.)

Medical Aspects of Traffic Accidents: Proceedings of the Montreal Conference. Edited by Harold Elliott, M.D. 8°, cloth, 519 pp., with illustrations, tables and charts. Montreal: The Traffic Accident Foundation for Medical Research, 1955. $7.00.

NONCLINICAL NOTES

AMERICAN HEART ASSOCIATION

Dr. Robert W. Wilkins, of Newburyport, was named president-elect of the American Heart Association at its annual meeting in Cincinnati, Ohio, on October 31. Dr. Wilkins, formerly president of the Massachusetts Heart Association, is chief of the Heart Service of the Massachusetts Memorial Hospitals and professor of medicine at Boston University School of Medicine.

BENJAMIN WATERHOUSE MEDICAL HISTORY SOCIETY

The Benjamin Waterhouse Medical History Society announces the election of the following officers for the year 1956-1957: president, Dr. Charles W. Robertson; vice-president, Dr. Elizabeth K. Moyer; and secretary-treasurer, Dr. John J. Byrne.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Dr. LeRoy Allen Schall, of Boston, was chosen president-elect of the American Academy of Ophthalmology and Otolaryngology during its annual convention at the Palmer House, Chicago, October 14-19.

Dr. Schall is professor of diseases of the ear, nose and throat, Harvard Medical School, chief of otology and laryngology, Massachusetts Eye and Ear Infirmary and Massachusettts General Hospital, and W. A. LeCompte Professor of Otology and Laryngology, Harvard Medical School.

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The House Officers' Association of the Boston City Hospital announces a previously unsubmitted lecture in the evening lecture series to be held in the New Cheever Amphitheater, Dowling Building, Boston City Hospital, on Monday, December 3, at 7 p.m.

Dr. G. A. Martini will speak on the subject "Skin and Liver Disease."

INTERNATIONAL ACADEMY OF PROCTOLOGY

An all-day seminar on coloproctology, sponsored by the International Academy of Proctology, will be held at the Hotel Kenmore, Boston, on Saturday, December 15.

Further information may be obtained from Dr. Frank Ciampa, 54 Highland Avenue, Somerville 43, Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 26. Benjamin Waterhouse Medical History Society. Page 971, issue of November 15.

NOVEMBER 26–29. Consultation Clinics for Crippled Children in Massachusetts. Page 828, issue of October 25.

NOVEMBER 27 and 29 and DECEMBER 4 and 18. Boston City Hospital House Officers' Association. Page 875, issue of November 1.

NOVEMBER 28. Phi Delta Epsilon. Page 831, issue of October 25.

NOVEMBER 28. Middlesex County Sanatorium. Page 831, issue of October 25.

NOVEMBER 28 and DECEMBER 12. Walter E. Fernald State School. Page 728, issue of October 11.

NOVEMBER 28–30. American College of Cardiology. Page 731, issue of October 11.

DECEMBER 1–15. Bahamas Medical Conference. Page 923, issue of November 8.

DECEMBER 2. American Academy of Dental Medicine. Page 923, issue of November 8.

DECEMBER 3. Boston City Hospital House Officers' Association. Notice above.

DECEMBER 7 and 8. Association for Research in Nervous and Mental Disease. Page 923, issue of November 8.

DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.

DECEMBER 15. International Academy of Proctology. Notice above.

JANUARY 17, 1957. Arthritis Study Unit. Page 831, issue of October 25.

APRIL 27, 1957. Postgraduate Medical Institute. Page 785, issue of October 18.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 29

THURSDAY, NOVEMBER 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.

8:00–9:00 a.m. Medical Journal Club. Joslin Auditorium, New England Deaconess Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00 a.m. Neurological Rounds. Dr. Kane. Evans 2 Conference Room, Massachusetts Memorial Hospitals.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*10:15 a.m.–12:00 m. Medical Grand Rounds. Dr. Keefer. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.

*10:15 a.m. Clinicopathological Staff Conference. Massachusetts Memorial Hospitals.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Metabolic Studies in Mitral and Aortic Stenosis. Dr. H. V. Parker. Main Amphitheater, Peter Bent Brigham Hospital.
*3:30 p.m. Gastroenterology Conference. Dr. Ingelfinger. Massachusetts Memorial Hospitals.
*7:00 p.m. Boston City Hospital House Officers' Association. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

FRIDAY, NOVEMBER 30
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*11:30 a.m. Tumor Clinic. Drs. Soutter and Lemon. Robinson 4, Massachusettts Memorial Hospitals.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, DECEMBER 1
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*9:30 a.m.–12:00 m. Grand Rounds. Haynes Memorial Hospital, Brookline.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, DECEMBER 3
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Tumor Conference. Dr. C. C. Lund and members of the Tumor Board. Dowling Amphitheater, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Staff Meeting. Obstetrical and Gynecological. Drs. Abrams and Parker. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Long-Acting Local Anesthetics. Dr. Thomas K. Burnap. Surgical Conference Room, Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon. Stearns Auditorium, New England Center Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference of Greater Boston. (A) Recovery Room. (B) Intensive Therapy Unit. Dr. Marcus. Auditorium, Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

TUESDAY, DECEMBER 4
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Gastrointestinal or Allergy Conference. Dr. Stanley or Dr. McCombs. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Medical Pathological Conference. Massachusetts Memorial Hospitals.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*2:00–3:00 p.m. Surgical Pathological Conference. Dr. Sheldon C. Sommers. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, DECEMBER 5
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Dr. Smithwick. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Understanding Character Neuroses. Dr. Irving Kaufman. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Craney. D-Main, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*1:00–2:00 p.m. Surgical Staff Meeting. Dr. Smithwick. Evans Conference Room, Massachusetts Memorial Hospitals.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00 p.m. Vascular Rounds. Robinson 4, Massachusetts Memorial Hospitals.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*6:30 p.m. Lahey Clinic Lecture. Portal Hypertension. Dr. Cornelius E. Sedgwick. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.